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New Insights into Anxiety Disorders

Edited by Federico Durbano

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Notice

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Meet the editor

Dr. Federico Durbano, was born in Genua, Italy, in 1963. He received degree in Medicine at University of Milan, Italy (Bicentennial on French Revolution). At the same University he had the specialisation in Psychiatry, and he became specialist in Forensic Psychiatry. Since 2001, he is the coordinator of the Emergency Psychiatric Service of Fatebenefratelli Hospital in Milan, Italy. Dr. Durbano is teacher at the Nursing School of University of Milan, and at the Criminology Master of C. Cattaneo University of Castellanza (Italy). He was speaker at more than 50 national congresses and teacher in more than 50 training courses. So far Dr. Durbano published about 120 papers on psychiatric issues.

Contents

Preface

The contributing authors have done their best to be clear and exhaustive enough about their topics. I will give a brief panorama on the structure of the work, just to introduce the chapters accepted for this publication.

Anxiety and panic disorders have now reached the size of a pandemic: a third of the western world and a substantial part of that global world that is facing to the modern (western) world suffer of pathological anxiety more or less seriously. According to NIMH data, onset of anxiety disorders is the earliest of all mental disorders (11 yrs age), and the 12-months prevalence in USA is 18.1% of adult population (of them, about 23% is graded serious or very serious). Women overtake men by 60%. And in the last decade, the whole world has experienced a series of man-made and natural disasters. Large numbers of people have therefore been exposed directly or (peculiarity of the modern world) via mass-media to potentially traumatic events, increasing dramatically the importance of anxiety in modern world. According to these data, the questions about what is the meaning of the phenomenon and what should be its management is an increasing measure of the inefficiency of the current therapeutic approaches, individually oriented and based on old approaches to an expanding and less and less individual problem.

We must bear in mind, however, that fear and anxiety are normal part of life. You may feel anxious before you take a test or walk down a dark street. This kind of anxiety is useful and adaptive - it makes you more alert or careful, saving your life in certain circumstances. Normally, it ends soon after you are out of the situation that caused it. But for millions of people, this anxiety does not go away, and gets worse over time, leading to a general malfunctioning of their somatopsychic integrity. The first part of this book therefore describes very well and very deeply the evolutionary meaning of anxiety and the adaptive value of anxious emotions. According to ethology, anxiety is a normal reaction to stress being actually beneficial in some situations. For some people, however, anxiety can become excessive, and while the person suffering may realize it is excessive they may also have difficulty controlling it and it may negatively affect their day-to-day living.

The chapters of the second part of the book are centered on the biological basis of anxiety, specifically on the role of the increasingly understood role of the “black box” cerebellum and of the alert circuits, of the disregulation of neuroendocrine functioning in personality disorders associated with anxiety behaviors, and of the role of inflammatory mediators in anxiety reactions; these are the most recent evidences on the developments of basic research on anxiety disorders, and are all written by clinical psychiatrist, under-

lining the importance that basic research has gained in recent years for an effective and efficient clinical practice.

After that, a third section explores some emerging clinical problems associated with anxiety disorders. A very interesting one is the description and discrimination of social anxiety and psychosis, very often social anxiety being confused with interpersonal hypersensitivity and some forms of paranoia. But also social anxiety is a dimension of paranoia, and a correct definition of the problem is of main interest for a correct therapeutic intervention. Being social anxiety an increasing problem affecting modern society, and being at the basis of drug abuse consumption and of other dissocial behaviors in order to counteract it, great efforts have spent to understand the concept of social anxiety, and a very important issue of research is about expressing and understanding emotions. The theme is very well developed in the third part of this book, exploring the peculiar modalities with which social anxious people express negative emotions and are unable to understand their inner positive emotions and beliefs. Another important issue regards the connection between anxiety and physical illness, specially because the main symptomatic expression of anxiety is physical (muscular tension, cardiovascular hyperactivation, vegetative symptoms). A particular aspect of modern psychosomatic research is the etiopathogenetic correlation between anxiety development and expression in some "medical" illnesses: one chapter of this book describes the correlation between inflammatory diseases of connective tissue (joint hypermobility syndrome), another one describes the peculiar manifestations of anxiety in prepartum and puerperium (exploring the most recent data on pharmacological treatment in these delicate periods of women life), and another chapter presents the problems of treating anxiety in personality disorders.

The last part of the book is therapeutically oriented. A lot of efforts have spent to achieve some results in PTSD, facing the increasing exposure to dramatic and terrifying events in modern world (television transmitted wars and natural disaster has a great role in the exploding and expanding manifestations of PTSD, or at least in hypersensibilize people). Here a clinical research group faced the consequences of Japanese tsunami, and tried to found an efficient and efficacious treatment to be administered in a short time to a great number of people in order to counteract the potentially pathological effects of a disaster. Another chapter describes the state of the art of hypnosis, trying to give some explanations about its mechanisms of action and efficacy; another one describes the psychological treatments of OCD, with a clear CBT oriented position, but describing also the limitations of some cognitive-behavioral approaches using evidence based methods. Last but not least, a chapter is centered on the unmet needs of the treatment of anxiety.

As the reader can see, there is a sort of red line which connects the different topics covered by this publication: anxiety as a normal psychological condition, but with potential pathological outcomes especially in the social domain (relational – social anxiety; functional – personality disorders; ambiental – PTSD), not forgetting the ones in physical functioning.

All the authors (all clinicians, I wish to remember) made their best to fulfill the objectives of this collaborative publication, and to all of them a special thanks for their work and for their contribution to an increase of scientific knowledge deeply rooted in clinical practice, which is what everyone of us needs in his daily practice.

A special thanks to InTech, too, which gave the possibility to have this publication and efficaciously supported the authors in the editing process.

Have a good reading.

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Section 1

General Issues

Chapter 1

An Evolutionary Perspective on Anxiety and Anxiety Disorders

John Scott Price

Additional information is available at the end of the chapter

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1. Introduction

Anxiety and depression are two of the negative emotions described by Levenson (1994). These emotions, along with anger, tend to disrupt the emotional homeostasis of the body, while the positive emotions such as contentment tend to restore homeostasis. The actions of anxiety and depression may be synergistic but they differ in important respects. Anxiety usually has an obvious cause and also a goal (safety, and the avoidance of danger), whereas depression usually has no obvious cause and also has no goal. Depression is thought to be related to social factors in relation to other human beings, whereas anxiety is related partly to social situations but also to non-social dangers. The strategies for dealing with human danger include submission, whereas this is not an appropriate response to non-human danger. Anxiety is classically thought to be concerned with the threat of danger, whereas depression is thought to be the result of danger. I will describe later how the negative emotions can be divided into the escalating emotions such as anger and the de-escalating emotions of anxiety and depression

In a recent monograph, Bruene (2008) says, "Behavioral observation of patients with anxiety disorders suggests that these disorders – as a group – reflect exaggerated responses to internal or external signals of perceived danger or threat. The autonomic part of the anxiety response pattern prepares the organism for one of several response options to terminate the anxiety-eliciting situation, namely, flight, immobility, submission or aggression."

An evolutionary approach to any behaviour (including anxiety and other forms of psychopathology) refers to two separate "causes". One is the question of function. What is the function of this behaviour, if any? Why has it evolved? What adaptive advantage does it give to the individual, or the individual's close kin, or to the individual's social group? This approach relies on behavioural ecology, which is the study of the function of behaviour, and

the evolution of alternative behavioural strategies (Troisi, 2005). The other question is its phylogenetic origin. How did it evolve in our ancestors, and does it occur in other species? Clearly the fossil record does not record anxiety, and whether it occurs in our immediate-return hunter-gatherer ancestors has not been adequately studied. So the occurrence of anxiety in other species is of interest, bearing in mind that behaviour can be very different in closely related species, such as the absence or presence of paternal behaviour in some rodents (e.g., montane vs. prairie voles).

These two questions, the function of behaviour and its phylogenetic origin, are two of the four questions which Tinbergen famously asked of any behaviour in order to understand it properly (Tinbergen, 1963): What is its function, what is its phylogeny, what is its ontogeny, what is its immediate causation? Of course, statements about the function of a behaviour during evolution are in a different logical category from statements about proximal causation, in that they cannot be verified empirically. This has led to negative comments from some sources (e.g. Dubrovsky, 2002), caricaturing them as "just-so stories", in the same category as Rudyard Kipling's "How the leopard got its spots"; but if we did not ask how the leopard got its spots, we might know a lot less about camouflage, colour vision and predator-prey relations,

I wrote on this topic ten years ago, and since what I said than can be read free on the internet (Price, 2003) I will try not to repeat myself, but rather emphasise certain points and attempt to cover more recent thinking.

2. The adaptive function of anxiety

It is obvious that anxiety is adaptive in protecting the individual from danger. A person who crossed Niagara Falls on a tightrope every day would not last long. In the UK we have had many deaths from "tombstoning", which means jumping off a high cliff into water (and entering it vertically, like a tombstone). Anxious avoidance of snakes and spiders has clearly saved lives, and the fact that there is no in-built anxiety about cars and electric sockets indicates that evolution has not had time to build up anxiety about these dangers. This is because of a "mismatch" between the present and the Era of Evolutionary Adaptation (EEA), which is the evolutionary time in which adaptations evolved.

I will write about the triune brain (McLean, 1990; Ploog, 2003). Although Paul McLean's ideas have been trashed by his successors in neuroanatomy (Wikipedia), and they do not fit well with the neuroanatomy of vocalisation (Newman, 2002), I think that some of his ideas are helpful, especially his idea of the forebrain consisting of three "central processing assemblies", operating somewhat independently, and arranged in a rostro-caudal sequence in the mammalian forebrain. This triune brain may well underlie the triune mind postulated by philosophers such as Plato, Pascal and Gurdjieff. Although I discussed this matter ten years ago, there is more to be said. One important finding is that the genetic tendency to generalised anxiety disorder (GAD) and major depressive disorder is the same (Kendler et al., 1992; Hettema et al., 2005), and so from an evolutionary view the arguments for one apply also to

the other. My own view is that anxiety and depression operate synergistically to manage social change in small groups, but more of that in a later section.

First, I will illustrate how escalation and de-escalation can be hypothesised to occur relatively independently at the three levels of the triune brain. Each level makes its own decision, when confronted by a threat or challenge, either to escalate or de-escalate:

Brain level	Response	to	threat
	Escalate	or	De-escalate
Rational level (isocortex)	Decide to fight (stubbornness or courage)	or	Decide to flee or submit (common sense)
Emotional level (limbic system)	Anger, feel assertive and confident	or	ANXIETY, feel inferior , impotent,
Instinctive level (basal ganglia)	Elevated mood	or	Depressed mood Anxious mood, GAD

Table 1. Escalating and de-escalating strategies at three brain levels: agonistic competition.

Human competition is very different from animal competition, and most of the methods of competition do not involve face-to-face encounters with rivals. Moreover, success is achieved not by intimidating a rival, but by attracting positive responses from other members of the group, resulting in prestige. Remarkably, the choices between escalation and de-escalation have survived the transition from agonistic to prestige competition, and so we can emend Table 1 to express the new type of competition, as laid out in Table 2:

Brain level	Response	to	competition
	Escalate	or	De-escalate
Rational level (isocortex)	Adopt new goals, actively pursue existing goals, assert oneself, speak in public	or	Give up goals, efface oneself, refrain from public speaking
Emotional level (limbic system)	Feel assertive, exhilarated and enthusiastic	or	ANXIETY, feel inferior, ashamed, writer's block
Instinctive level (basal ganglia)	Elevated mood	or	Depressed mood Anxious mood, GAD

Table 2. Escalating and de-escalating strategies at three brain levels: prestige competition.

It should be clear that de-escalation at the rational level can pre-empt or terminate de-escalation at the lower levels. These lower levels have evolved as a safety net in case the rational brain is too ambitious. Therefore we often see patients who are escalating at the

rational level, but, their escalation being unsuccessful, the lower levels are accessed. We also see patients who are escalating at the emotional level, and in spite of de-escalation at the rational level, if the angry emotion does not achieve its aim, we then get de-escalation at the instinctive level. Most of these patients have suffered unjustified misfortune, such as death of a child or being passed over in work by an incompetent member of the family firm; they are denied the principle of retributive justice, as was Job in the Book of Job of the Old Testament.

The idea of separating the negative emotions into escalatory and de-escalatory is not new. Stone (2002) reports that "Maurice de Fleury (1897) divided the emotions into two groups. Doubt, humility, sloth, fearfulness, sadness and pity are symptoms – to varying degrees – of cerebral exhaustion; Pride, foolishness, anger, egoism, courage, heroism, and cruelty are the manifestations of exaltation of the spirit." (p. 9).

2.1. The anxiety-generating effect of bad news

I would like to re-emphasise the importance of "bad news" in the genesis of psychopathology, as this does not seem to be generally recognised. Bad news, of deaths and other disasters, is not available to our primate cousins who are not equipped to exchange gossip, but has been available to our ancestors over the last few million years since language evolved. Since these ancestors lived in groups of about 150 individuals, the amount of bad news they could generate was limited, even if we add in bad news from neighbouring groups. Now, we have available the bad news of many billions of people. Since news of death or other disaster may presage the nearby existence of a predator or of raiding parties from neighbouring tribes, or of disease, it must have been adaptive for bad news to increase anxiety and promote activities to ward off occurrence, such as increased washing, checking of security arrangements, and the advantageous territorial constriction of agoraphobia.

In the EEA bad news was probably discussed and so shared with other group members, whereas modern man tends to watch it or listen to it on his own, or at least without comment. Things are worse when the bad news is close by. An Egyptian psychiatrist (Nagy, 2012) reports on a patient who was glued to her TV set, absorbing the chaos all around her; and the situation was dire: two of the psychiatrist's students were killed while trying to save injured protesters.

When I practiced as a clinician, I advised all my anxious patients to avoid watching TV news, and I found that many of them had learned the lesson for themselves. They realised that each item of bad news raised their background level of anxiety, and, of course, severely depressed patients may believe that they are personally responsible for the disasters which occur daily around the globe.

There is a need for controlled study of the effect of reducing patients' access to bad news, and this is difficult in modern conditions when family television has replaced games and conversation for family interaction. I make a point of advising my anxious patients to restrict their viewing to comedies and nature programmes, although this injunction may cause family arguments, if other members of the family have a different viewing agenda. This is

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yet another argument for treating patients in family groups, so that the whole family can be motivated to protect the patient from the horrors of contemporary life. No one, to my knowledge, has done a controlled trial of "news avoidance" as an item of therapy.

2.2. Growing up with anxiety

A lot of variation in neuroticism (the personality equivalent of anxiety-proneness) is due to genetic factors and to non-shared environmental experience, negating the folk psychology view that children are strongly influenced by the behaviour of their parents and the atmosphere of the family home. Some genotypes prosper under negative home circumstances, whereas others suffer under those circumstances, but prosper more than the "tough ones" when the environment is benign (Bruene et al., 2012). This confirms the old observation that some children do better with the stick, and others with the carrot. We need to improve our means of distinguishing these two genotypes early in childhood.

I will say something about the genesis of anxiety in adolescence. Much good work has been done on the establishment of a secure base for the child in infancy (Price, 2000), but less has been done on adolescence, which in my clinical experience is a strong divider into the happy and the miserable. Some young people take to adolescence like a duck to water, and they are accepted by their adolescent peers and given positions of influence and even leadership in their groups. Others do badly at this time, and are bullied unmercifully by both boys and girls, that by boys tending to be physical, that by girls tending towards social exclusion. Normal children entering adolescence may be disadvantaged for many reasons; they may be odd in some way, speak with an unusual accent, have some physical deformity, or maybe they have moved into an area where the adolescent group is already full and does not want new recruits. For those who have suffered anxious or avoidant attachment in infancy, the problems of adolescence are compounded (Wilson, Price & Preti, 2009).

2.3. Social anxiety disorder (SAD)

Social anxiety disorder (SAD) is an exaggeration of the normal submissive or appeasement display which people make to more powerful individuals or to a disapproving group. Kaminer and Stein (2005) point out that SAD is an excessive fear of humiliating or embarrassing oneself while being exposed to public scrutiny or to unfamiliar people, resulting in intense anxiety upon exposure to social performance situations. Feared social situations are either avoided as much as possible or create significant distress. Physical manifestations of anxiety in the feared situations include a shaky voice, clammy hands, tremors and blushing. In the generalized sub-type of SAD, anxiety is associated with most social situations (including both formal performance situations such as giving a speech or speaking at a meeting, and informal social interactions such as initiating conversations, attending parties or dating); in the non-generalized sub-type, anxiety occurs only in specific social situations, such as public speaking, or eating/drinking in public, or writing in public. Prevalence rates for SAD range from 3% to 16%. From an evolutionary point of view, SAD must promote group functioning by reducing social competition, and ensuring that group discussions in the council chamber do not last indefinitely. Most readers will be aware that in question time

after a scientific paper, the people who ask questions are those who have social confidence and like the sound of their own voices, regardless of their knowledge of the subject, whereas many of those with something important to say remain silent because of SAD.

3. Anxiety in other species

Anxiety is the emotion associated with avoidance of danger, and it is obvious that many species encounter more danger than ourselves. Humans are sometimes taken by tigers and other predators, but many species are subject to constant predation, being the basic diet of the predator species. Can we learn from their reactions? One obvious defensive measure is to have a safe haven, especially at night. Some species avoid danger by being enclosed, others by being exposed. An extreme example of being enclosed is the naked mole rat, which does not appear above the surface of the earth. Rabbits avoid danger to their young by visiting them for suckling only once a day, and ferrets are more extreme in suckling only once in 48 hours. In this way they avoid giving predators a clue as to the whereabouts of their burrow, and this advantage clearly outweighs the advantage of constant maternal care. When kept in cages, rabbit and ferret mothers cannot do this, which may account for some of the aggressiveness they show at this time. Some species prefer to be exposed, such as the hamadryas baboon which sleeps on a cliff face, and many birds nest on cliffs for the same reason. Some humans adopt both strategies, and live in caves which open onto the cliff face, and in this case either acrophobia or claustrophobia would be a disadvantage.

A lot of information about animal anxiety is available informally on the internet: just Google "anxiety in horses (or monkeys, or birds, etc.)". Different animals have different sources of anxiety and different reactions to it; for instance, horses suffer from severe separation anxiety, and this no doubt originated in their need to stay with their herd.

Some group-living species delegate the role of anxious individual to one of their members, so that the rest can forage free from anxiety. We have all seen films of meerkats in which the group forages happily while one member stands on a mound and looks anxiously for birds of prey and terrestrial predators. This delegation of responsibility may be important for humans. If a foraging meerkat does not trust the sentry, the freedom from anxiety may be lost. If the obsessional housewife does not trust her cleaning lady, she is likely to repeat the work while nursing pathological grievance against her employee.

3.1. Phylogeny of anxiety

In an intriguing chapter, Hofer (2002) describes the response to danger in organisms of varying complexity. The bacterium swims forward with its flagella working together, absorbing molecules of sucrose and other foodstuffs. However, if receptors on its surface detect a toxin, its flagella then act independently, and the bacterium tumbles about. In half a second, it has forgotten about the toxin and sets off with flagella all pulling together, in whatever direction it happens to be pointing at the time. Hofer comments: "When it stops and tumbles in response to the presence of a negative signal, is it anxious? Certainly, we would not want

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to say so, even though the mental picture of a tumbling creature with flagellar hairs standing on end may be intuitively persuasive…..The presence of these behaviors in so primitive an organism gives us an idea of how basic a state resembling anxiety has been for survival of life forms."

Hofer also discusses the invertebrate sea hare, *Aplysia californicus.* It can be conditioned to respond with avoidance to shrimp juice by associating it with electric shocks (mimicking its predator, the starfish), thus producing a state of anticipatory anxiety, but in the absence of shrimp juice (the conditioned stimulus) its behaviour is normal. However, a series of uncontrollable electric shocks produces a "persistent state (lasting several weeks) in which defensive and escape responses were exaggerated, and responses to positive events were blunted, an abnormal behavioral repertoire had been established that resembled a form of chronic diffuse anxiety."

The development of the limbic system in mammals allowed new and social forms of anxiety to evolve. Rat pups emit high frequency squeaks when separated from their mother and these sounds release searching and retrieval behaviour in the mother. In his own work, Hofer was able to breed strains of rats with high and low tendency to emit squeaks. He speculates that the ability to squeak evolved to keep the rats warm, and only secondarily became a signal to the mother (exaptation). The squeaks are inhibited by benzodiazepines and opioids, and exacerbated by benzodiazepine antagonists. In later work (Brunelli & Hofer, 2007) the high squeak infant rats developed into nervous adults, while the low squeak rats were notable for their aggression, so there had presumably been selection for escalation versus de-escalation in the emotional (limbic) forebrain. Presumably, rabbit and ferret pups do not respond to separation in this way, otherwise they would attract predators to their burrow.

Turning to primates, Hofer describes Suomi's work on free-ranging rhesus macaques on an island in the Caribbean. This population contained a sub-population of very anxious individuals, some of whom suffered from "lasting incapacitating states resulting in substantial mortality". The anxious traits could be increased by selective breeding and prevention of good mothering. He describes the response to "chronically threatening conditions. Persistent anxiety (high levels of arousal, searching for cues for danger, and high levels of avoidance of potentially damaging encounters) confers an adaptive advantage over less anxious individuals." There has been criticism of Suomi's work on humanitarian grounds.

In the case of humans, Hofer describes the speculation of Klein that panic attacks may be a response to imminent suffocation, mediated by high levels of blood carbon dioxide. Hyperventilation (overbreathing) is a common feature of panic attacks, and may aggravate the panic by causing tetany due to low levels of carbon dioxide and thus an excessively alkaline blood.

My own extensive experience of patients with panic attacks resulted from an appointment as medical casualty officer in a hospital near an underground railway station in London. Two or three patients a day were brought by ambulance from the station, having developed panic in the underground, especially when it was crowded and the train stopped between

stations. These patients had very rapid respirations which caused involuntary contraction of muscles and sensations of tingling due to the alkalinity of the blood due to loss of carbonic acid due to overbreathing. Of course, these symptoms aggravated the panic and most of the patients thought they were dying. Their condition was rapidly cured by getting them to breathe into a paper bag, so that they were rebreathing their own carbon dioxide. Talking to these patients when they had recovered, it was clear that most of them were healthy young adults who had no history of excessive anxiety or any other psychiatric disorder.

Hofer concludes by pointing out that patients may benefit by being told that they are suffering from, not madness, but from a mechanism that has enabled their ancestors to survive the dangers of our evolutionary past.

4. Genetics

A lot of excitement has been caused by the discovery of a polymorphism in the serotonin transporter gene (which enables the reuptake of serotonin into the presynaptic neuron),because most of our effective antidepressant drugs inhibit the reuptake of serotonin. Equally exciting is the possibility that there is a gene/environment interaction in its effect (Risch et al., 2009). It has been suggested that the "short" allele of the serotonin transporter coding gene is associated with greater risk for depression if linked with early childhood adversities, yet the same version of the gene is associated with *reduced* risk for depression if carriers grow up in emotionally secure conditions (Belsky & Pluess, 2009). This suggests that selection favoured plasticity or "open programs" that render individuals more susceptible to environmental contingencies – for better *and* worse (Belsky, Jonassaint & Pluess, 2009). Similarly, psychiatrists guided by evolutionary theory have recognized that antagonistic pleiotropy may play a role in psychiatric disorders – genes that convey fitness advantages in one domain, while having potentially maladaptive value in another domain, a concept that was originally put forth with regard to senescence (Bruene et al., 2012). Nowadays, examples for antagonistic pleiotropy can be pinned down to even single genes such as the catecholamine-O-methyltransferase coding gene, of which one particular allele is associated with poorer working memory performance but superior empathy (Heinz & Smolka, 2006)). Taken together, these insights offer an answer to the question of why natural selection designed bodies that are – under specific circumstances – vulnerable to disease (Nesse & Williams, 1994). There have been several hundred studies of the serotonin transporter gene in various psychiatric populations and consistent results are not easy to obtain (Duncan & Keller, 2010).

I mentioned above some findings from the large Virginia twin study carried out by Kendler and his colleagues (Hettema, Prescott, Myers et al., 2005). They found that the genetic predisposition to major depressive disorder was the same as that to generalised anxiety disorder and to panic disorder. There was some overlap with social anxiety disorder and agoraphobia, but the genetic predisposition to specific phobias was separate. This means that if one is predisposed by genetics to major depressive disorder, one is

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equally predisposed to general anxiety disorder (GAD), but the same cannot be said for lesser degrees of anxiety.

4.1. The serotonin transporter gene in macaques.

Humans and macaques are the only primates to have the short version of the serotonin transporter gene. 48% of Caucasian populations are heterozygotes, having both short and long alleles. 36% are homozygotes for the long allele, 16% for the short allele. Rhesus monkeys who possess the short allele are notably more anxious than the long homozygotes (Watson et al., 2009). Moreover, when shown pictures of dominant monkeys, their pupils dilate more than those who are homozygous for the long allele, and they have to be bribed (with juice) to see the face of a dominant monkey, whereas the long homozygotes will forego juice in order to see the same pictures. The rearing of these monkeys is not described, so it is difficult to compare with the human data mentioned above.

4.2. Anxiety in different human cultures

I am not an anthropologist, but it is clear from the literature that some cultures have different attitudes to anxiety and maybe different genetic predispositions. Margaret Mead (1935) studied three tribes living in the Sepik River Valley of Papua New Guinea. The Mundugumor were very aggressive and warlike, so that anxiety was not a desirable feature with them (but the actual frequency of anxiety is not known). The Arapesh were extremely peaceful. The Tchambuli were also peaceful and the men spent their time putting on plays. The two latter tribes had been driven out of the fertile areas of the island.

The Tarahumara of Mexico (McDougall, 2010) are reported to be extremely nervous and inhibited, so that any social contact requires large quantities of corn beer to be consumed. They are famous for their utrarunning (running more than marathon distances), and possibly they seek the "runner's high" (thought to be due to the release of endogenous opioids) to counter their natural timidity.

Also very nervous are the Chewong of the Malaysian Peninsular, and in this tribe the admired norm of behaviour is to be timid (Howell, 2012). It is said that the elders are fond of telling stories about the times they have run away. Asiatics may have higher frequencies of the short version of the serotonin transporter gene than Europeans (Watson et al., 2009).

5. Anxiety and its resolution in a sacred text

For reasons of confidentiality, we cannot present case histories from our practice, but fortunately there is a clear account of an anxiety attack and its resolution in the Hindu epic poem, the Mahabharata (Price& Gardner, 2009). The poem describes a long and bitter struggle between two sets of cousins, the Pandavas and Kauravas, for control of ancestral lands. The Bhagavad Gita (a small part of the Mahabharata) begins with the two armies drawn up for battle with warriors blowing conches and beating drums. Arjuna, a younger Pandava broth-

er renowned as an archer, drives his chariot between the armies to assess the opposition. His charioteer is none other than the god Sri Krishna. As Arjuna views the superior Kaurava army, he sees relatives and mentors he knows well. He feels doubts about killing these family members and friends, translated by Mitchell (2002) as follows:

Arjuna saw them standing there: fathers, grandfathers, teachers, uncles, brothers, sons, grandsons, fathers-in-law, and friends, kinsmen on both sides, each arrayed against the other. In despair, overwhelmed with pity, he said: "As I see my own kinsmen, gathered here, eager to fight, my legs weaken, my mouth dries, my body trembles, my hair stands on end, my skin burns, the bow Gandiva drops from my hand. I am beside myself, my mind reels. I see evil omens, Krishna; no good can come from killing my own kinsmen in battle. I have no desire for victory or for the pleasures of kingship" ….. Having spoken these words, Arjuna sank down into the chariot and dropped his arrows and bow, his mind heavy with grief…..

As Arjuna sat there, overwhelmed with pity, desperate, tears streaming from his eyes, Krishna spoke these words to him: "Why this timidity, Arjuna, at a time of crisis? It is unworthy of a noble mind; it is shameful and does not lead to heaven. This cowardice is beneath you, Arjuna; do not give in to it. Shake off your weakness. Stand up now like a man."

Arjuna said: "When the battle begins, how can I shoot arrows through Bhishma and Drona, who deserve my reverence? …… I am weighted down with pity, Krishna; my mind is utterly confused. Tell me where my duty lies, which path I should take. I am your pupil; I beg you for your instruction. For I cannot imagine how any victory – even if I were to gain the kingship of the whole earth or of all the gods in heaven – could drive away this grief that is withering my senses."

Having spoken thus to Krishna, Arjuna said: "I will not fight," and fell silent.

As Arjuna sat there, downcast, between the two armies, Krishna smiled at him, then spoke …

The god Krishna, the eighth avatar of Vishnu, then speaks to Arjuna for 16 more chapters (and the reader is left to wonder what the two armies are doing during this time). In a verbal dominance display of unparalleled beauty (except possibly for the speech of the Lord out of the whirlwind in the book of Job), Krishna explains to Arjuna that he is all-powerful, and then he displays himself to Arjuna in all his divine majesty. Arjuna is overwhelmed and submits to Krishna, saying "I will do as you command". He then recovers from his anxiety attack and fights heroically in the ensuing battle.

In this example we see a distressing situation lead to a severe panic attack, a request for advice which is not followed, a dominance display by the god followed by total submission on the part of Arjuna and then recovery from anxiety. By abrogating responsibility to Krishna at the rational level of his triune mind, Arjuna no longer needs the anxiety which arose from his emotional mind due to the initial failure of the rational mind to deal with the problem (by taking Krishna's advice).

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5.1. Anxiety and art

Although artists can portray frightening scenes, it is less easy for them to depict the anxiety response. Here is a comment by Edvard Munch about his famous (and expensive) painting "The Scream":

"I was walking down the road with two friends when the sun set; suddenly, the sky turned as red as blood. I stopped and leaned against the fence, feeling unspeakably tired. Tongues of fire and blood stretched over the bluish black fjord. My friends went on walking, while I lagged behind, shivering with fear. Then I heard the enormous, infinite scream of nature." He later described the personal anguish behind the painting, "for several years I was almost mad… You know my picture, 'The Scream?' I was stretched to the limit—nature was screaming in my blood… After that I gave up hope ever of being able to love again." (Wikipedia).

5.2. Social presentation of the anxious person

Anxious patients may not appear anxious to others, but may be seen as aloof or even arrogant. Leahy (2010) puts it as follows::

"People with social phobia or social anxiety often give out signals of their own apprehension that inadvertently send the wrong message. For example, many of my patients over the years with social anxiety often don't smile, they avoid eye contact, and they remain silent because they are so anxious that they will either sound foolish or look anxious. Ironically, these attempts to remain "closed" result in the "wrong impression". Many of these people appear to be cold and aloof-and, in some cases, conceited. It's the wrong message and they don't even know they are sending it. Ironically, they fear that they will appear anxious, but they actually appear arrogant. They also fail to "mirror" or "match" the emotions that others are displaying. For example, other people may be smiling, but the anxious person may remain cool and aloof. This sends the wrong message - that you are not interested and you don't care."

One of my first patients was just such a young man, seen as aloof by fellow patients in a neurosis unit (Sainsbury and Price, 1969). Asked to paint "Myself and the group" in art therapy, he drew a circle of red blobs representing the group and a single black blob representing himself. In the group discussion the next day, the other patients said that they had thought he felt himself superior to them, but in the ensuing discussion he disabused them of this idea and was then accepted by the group. This is similar to the misperception of depressed patients, who are seen, not as depressed, but as lazy because they do not perform tasks well, or rude because they do not carry out social obligations such as writing thank-you letters.

The concealment of anxiety is a promising line of study. A chimpanzee in a conflict situation has been seen literally wiping the submissive grin off his face with his hand. Some tribes cut the muscles around the mouth to prevent the manifestation of a trembling lip. The concealment and detection of anxiety is to be found expressed in the novels of Georgette Hayer. Anxious young people may hide their anxiety from their parents, perhaps hiding scars on

their forearms with long sleeves, and this may lead to further parental pressure to succeed academically which, of course, makes the anxiety worse. I described this situation in some detail in my previous paper (Price, 2003), and here I reproduce the figure which illustrates how the ambitious parents mistake the position of their child on the Yerkes-Dodson curve:

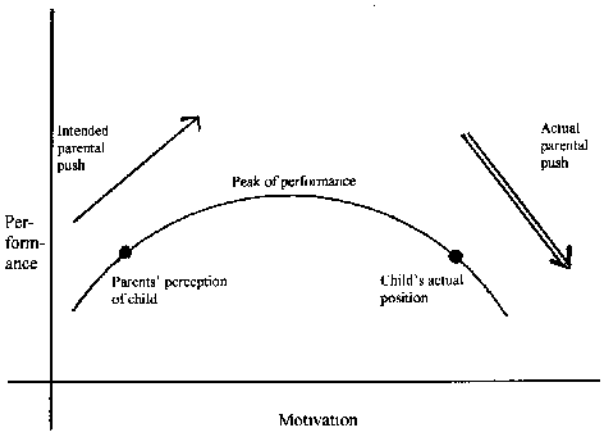

Figure 1. The inverted U-shaped curve of the Yerkes-Dosdon law. The single-shafted arrow represents the parents' attempt to push the child up towards the peak of performance. The double-shafted arrow represents the actual effect of the parental pushing.

6. Conclusion

Since evolutionary speculations are not directly testable, I have tried to show how they may be useful in planning treatment programmes, and in research. One of the main contributions of the evolutionary perspective is to show that anxiety plays a major role not only in protecting people from non-social dangers, but also in maintaining social stability in social groups. Practically all group-living vertebrates have social hierarchies which function to maintain peaceful relations within groups and also to provide a structure for social selection to occur. There is an enormous amount of inhibition in these animal groups, and this is maintained by anxiety and depression. Especially among males, life is one of continual inhibition, in which desires for mating, food and sleeping quarters are supressed. Few individuals achieve the alpha position in their groups, and it is only these alphas who are free to express their personalities and desires without inhibition. The acceptance of relatively low hierarchical position by other group members allows the group to work co-operatively, as in hunting by wolves and cape hunting dogs.

6.1. Rational de-escalation can prevent or terminate sub-rational de-escalation

Aristotle pointed out that if someone hits you, you experience pain; if the pain is caused by a higher ranking individual, you feel sad, if it is caused by a lower-ranking individual, you

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feel angry. You have no choice about these reactions as they are determined by the sub-rational brain. You do have a choice about your voluntary action. You can attack the person who hit you, and this is the fight version of the fight/flight response; or you can shrink away, and this is the flight version of the fight/flight response. If you attack a higher-ranking person, you are likely to incur severe costs; on the other hand, if you win, you stand to gain significant benefit. Since fight involves actions such as recruitment of allies, preparation of armaments and planning of strategy, it has been described as an escalatory response by behavioural ecologists; this contrasts with the de-escalatory response of flight which also includes submission, in which there may be not only an absence of flight, but an actual approach to the rival for the purpose of reconciliation. Therefore in a threat situation we have a choice between escalating and de-escalating strategies at two or more levels. With our rational brain we can choose either to fight or submit, and with our sub-rational brain we can "choose" either to feel angry or to feel sad and anxious. If these two brain levels choose the same strategy, then all is well, there is either angry attack or anxious submission. But if the two levels make opposite choices, there may be trouble. Especially if the rational brain decides on escalation and the subrational brain decides on de-escalation, we are in for trouble (psychopathology).

We do not have to go further than Charles Darwin himself for an example. His theory of evolution by natural selection was an attack not only on the church, but also on his wife (who held religious views). In pursuing his theory he was escalating at the rational level. His escalation was at first muted, since he kept his manuscript in a drawer for many years. But his attachment to the goal of publication was evidenced by his rapid response when a rival appeared in the form of Wallace, and he was quick to summarise his theory for joint presentation with Wallace to the Linnean Society. With encouragement from his friends, his rational response was escalation. But his sub-rational brain made a different analysis of the situation, seeing the church as a formidable rival and not one to be trifled with; therefore it made a decision to de-escalate. As a result Darwin was plagued with anxiety and psychosomatic symptoms for the rest of his life.

I have treated many patients who are escalating at the rational level but de-escalating at the sub-rational level. Reasons for rational escalation can be called courage or stubbornness, depending on your viewpoint. Moral scruples are a common cause for escalation; for instance, patients refuse to take part in stealing by fellow employees and so suffer social exclusion; one patient of mine refused to accept advertisements for call girls for her magazine, which put her in conflict with management. In our monograph, Stevens and I report in some detail the case of a porter who refused to take sick leave when he was not sick. The poet Milton (not a patient of mine!) continued writing poetry and tracts criticising the monarchy, and suffered ill-health as a consequence.

As can be seen from the Tables, the sub-rational brain can be divided into two, an emotional level in which there is partial realisation of the situation and an instinctive level in which there is no such realisation. Here again, escalation in the form of anger may be combined with de-escalation at a lower level in the form of depression and anxiety. If anger is effective in righting the situation, all is well, but often anger is frustrated by authority or by the situa-

tion itself, so that lower level de-escalation becomes chronic. Patients of mine in this situation include parents whose child had been killed by a drunken driver, people unjustly sacked form their jobs, parents whose children have been denied educational opportunity be the school system, and, in one remarkable case, a father whose daughter had precocious puberty and who was accused by social services of sexually interfering with her. Treatment in these cases is difficult. In some cases I have helped the patient to discharge the anger by writing letters to the offending authority. In some cases, joining a group with other people similarly abused can direct the anger into productive channels, as when group of parents whose children have been killed by drunken drivers band together to tighten the laws on drunken driving.

6.2. Delegation and abrogation

One clear suggestion from the evolutionary viewpoint is the desirability of shedding responsibility. This can take the form of delegation of responsibility to other members of the social group, and the model here is the adoption of the role of sentry by foraging meerkats. Also there is abrogation of responsibility to a more powerful person or a higher power. This is part of the programme of AA in which one "step" is to acknowledge that one cannot give up alcohol on one's own, without the help of a higher power, which may be some form of deity or an emergent property of the group. We have seen how Arjuna's panic attack and anxiety about killing his relatives and friends was allayed by submission to his God, Krishna. Many religions offer peace and joy to those who submit. One of my own anxieties is about the loss of rainforest in the world, and this anxiety is assuaged by my knowledge that Prince Charles is not only more worried about it than I am, but is also immensely more powerful.

The mismatch between the environment in which we evolved (the EEA) and the conditions we now live in are not difficult to apprehend. One crucial difference is the transmission of bad news. We now have daily reports of the tragedies and afflictions which affect many billions of people, whereas our ancestors knew only about the reverses suffered by a group of 150 or so people. Therefore it is sensible to encourage anxious people to avoid reading newspapers and watching news broadcasts, and stick to sport, comedy or nature programmes.

An evolutionary approach is also helpful for research, offering a wide variety of animal models of anxiety for the investigation of mechanisms and the testing of anxiolytics. There has been too little work on reptiles, some of whom change colour when defeated. Tail-chasing in dogs is being used as an animal model of obsessive-compulsive disorder (Tira et al., 2012).

6.3. Treating the anxious patient

Here is a check-list for the therapist who is treating an anxious patient:

1. Since from an evolutionary perspective anxiety is an unconscious form of submission, has the patient submitted consciously and voluntarily where necessary?

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2. If the patient is a believer, have they submitted totally to their god, or are there elements of "My will be done", or is there a problem with accepting a god who allows unnecessary suffering? If the patient is not a believer, has he accepted the universe and his place in it: if not, he should join a group of people with similar problems.

3. At work, does she respect her boss, or does she think she could do the job better? Does she have insubordinate subordinates?

4. Has he or she submitted to the reasonable demands of the marriage partner?

5. Has he submitted to the rules of society? E.g., does he avoid paying taxes or fiddle his expenses?

6. Has the patient delegated where possible, and does he or she trust the person delegated to?

7. Has the patient restricted television viewing to comedy and nature programmes?

8. Have you spoken to the patient's marriage partner or someone else close to the patient? Teenage or grown up children often see things that adults miss, and they usually appreciate being involved in their parent's treatment, especially if there have been threats of suicide.

9. Is the anxiety worse after receiving letters or phone calls or visits from anyone?

10. Has the patient got supportive friends? If not, group therapy should be considered (and also for patients who have been abused by the adolescent peer group – fellow group members can provide a re-run of the adolescent experience).

11. Are the patient's goals in life realistic?

12. Is there conflict with anyone such as a neighbour or relative?

13. Is there unresolved grief?

14. Is there a problem with alcohol or anxiolytic medication?

In the behavioural treatment of anxiety, there is an odd situation in which extremes may be more beneficial than anything in between. Thus the choice may be between very gentle deconditioning and flooding, in which the patient is kept in the anxiety-arousing situation for as long as it takes for the anxiety to subside, and then the patient realises they can be in that situation without anxiety. This is similar to the situation with autistic children, with whom success has been achieved either by a very gradual approach or by overwhelming cuddling. The same applies to self-esteem, which may be built up with the help of a therapist, or the self may be abnegated to facilitate total submission to God. Philosophers advise us to take the middle course, but sometimes the middle course is ineffective.

In summary, anxiety evolved to keep us out of danger, to obey the rules of our group, and to treat each other with respect. If we have too much anxiety, we suffer, if we have too little, we may become insufferable.

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Chapter 2

Anxiety: An Adaptive Emotion

Ana G. Gutiérrez-García and Carlos M. Contreras

Additional information is available at the end of the chapter

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1. Introduction

Anxiety as an adaptive response is a natural emotion that occurs in response to danger and prepares an organism to cope with the environment, playing a critical role in its survival. Among the components of anxiety, the expression of fear may inform other members of the group about the presence of imminent danger (i.e., an alarm cue). The environment is perceived by a filtering process that involves sensorial receptors. While coping with a stressful situation, an individual may simultaneously emit vocalizations, perform movements to escape, freeze, and deliver to the environment chemicals called alarm pheromones. These cues are recognized by the receptor-individual by specific sensory systems located in the legs and antennae in insects and olfactory sensorial systems in other organisms. In mammals, the sensorial information is integrated by anatomical and functional pathways, with the participation of structures related to emotional memory, namely deep temporal lobe structures. Some stimuli are perceived as relevant when they contain relevant meaning according to previous experience and learning. The participation of ventral striatum and prefrontal cortex connections then leads to the selection of an adequate strategy for survival. The perception of these cues by other individuals in the group establishes intraspecies communication and causes striking behavioral responses in the receptor subject, namely anxiety, but the consequence is likely different. While the emitting subject may be in an emergency situation that is perhaps devoid of a solution, the receptor subject may have the chance to cope with the dangerous situation by employing efficacious strategies, depending on previous experience. The aim of this chapter is to review the participation of such anatomical pathways, their neurotransmission systems, and the resulting behavioral patterns.

2. Expression of fear and anxiety as emotions

Emotions are transient events generated in response to some stimuli that produce arousal reactions and changes in motor behavior, subjective feelings, and subsequent changes in behavior [15]. Thus, emotions are cognitive and somatic reactions, with a short duration, to specific environmental stimuli [7]. In the case of an emergency situation, emotions give way to strategies that allow the survival of the individual and, therefore, the species. Emotional processes are crucial for the control of human behavior [15], and a failure in the management of emotions is a common denominator of a wide range of psychiatric disorders [22].

In broad terms, emotions are considered to have two dimensions. The first dimension is equilibrium, in which emotional states range from positive (i.e., happy or safe) to negative (i.e., fear or anger). The consequent behavioral responses depend on emotional states. For example, in a positive emotional state, there is a tendency to approach the stimuli, whereas negative emotional states are associated with aversion, defense, escape, and avoidance. The second dimension is arousal. Both positive and negative emotional states may vary from a relatively quiet attitude to high levels of restlessness [54; 53]. Examples include freezing in a passive attitude or escaping in more proactive coping patterns [20]. Emotions play a role in the daily lives of individuals, enabling them to cope with everyday situations.

Fear is a part of the anxiety syndrome. It consists of a feeling of agitation caused by the presence of imminent danger and may be considered a protective emotion. From an evolutionary point of view, however, its expression is very similar to anxiety as an adaptive emotion. An exception may be posttraumatic stress, an anxiety disorder in which fear is present even in the absence of the stimulus that elicited the original state of anxiety [100]. Notably, fear can be conditioned by various stimuli, and its study from different methodological perspectives has allowed a better comprehension of the underlying neurobiological processes of anxiety.

3. Is anxiety a disease or an adaptive response?

Anxiety comprises two related concepts. First, it is a disease. Second, it is an adaptive response. As a disease, anxiety is a highly disabling pathological condition, involving cognitive, emotional, and physiological disturbances. Its main symptoms include restlessness, increased alertness, motor tension, and increased autonomic activity [2]. In the long-term, the deleterious effects of anxiety on personal capabilities represents a considerable mental health problem. Generalized anxiety disorder is frequently associated with other pathologies, but it may constitute the only symptom in several manifestations, including panic disorder, posttraumatic stress disorder, and obsessive compulsive disorder [2]. It is one of the most common psychiatric disorders, affecting approximately 28% of the general population [49]. In México, as in other countries, it occurs more often in women than in men [64]. Typically, the symptoms last a long time, even when the stimulus has disappeared [100].

Adaptive anxiety may be considered a useful emotion that leads to survival strategies [4]. In this sense, anxiety is a normal emotion that occurs when an individual copes with a potential-

ly dangerous situation, constituting a mechanism for alertness or alarm [41]. In this case, the symptoms of anxiety, which are identical to the pathological condition, disappear once the stressful stimulus disappears. Meanwhile, in most cases, it leads to coping with the emergency situation. As the best strategy is chosen, the probability of ensuring survival increases.

One of the main differences between the two kinds of anxiety is the contingency of the response to the stimulus. Otherwise, pathological anxiety induces positive feedback, in which anxiety generates more anxiety [75] and, notably, spreads to other individuals in the group [88; 24]. The combination of feedback and the spread of anxiety can lead to a collective panic reaction that involves those individuals who surrounded the first individual who experienced anxiety [89], often with fatal results [74; 62]. One very special case is related to caregivers. Observing a state of anxiety that leads to deteriorated social functioning and health is common in caregivers, with undesirable effects in both the caregiver and patient [94]. Therefore, anxiety may be both a disease and an adaptive response that involves shared processes and in some cases may inclusively consist of a continuum.

4. Anxiety is contagious

In the case of anxiety as an adaptive emotion that leads to survival strategies, the spread of anxiety to other individuals in the group may offer warning signs that allow for the protection of other individuals and consequently the group and ultimately the species [6].

Generally, all stimuli derived from the environment initially undergo a sensorial filtering process in sensorial receptors, beginning with parareceptors [8], reaching synaptic relays, and leading to an integrative process that involves anatomical structures related to emotional memory [43], in which comparisons are made with older elements of memory [92]. As the stimulus inputs reach the striatum and cortical structures [43], a selection of the adequate survival strategy is often reached [34]. In turn, connections with motor areas and motoneurons activates skeletal muscles [43], and a motoric response may be observed. Laboratory animals subjected to a stressful situation (e.g., odors from a predator) will emit only a few responses—attacking, freezing, or escaping—no more and no less.

One important aspect is the meaning of the stimuli. Only a portion of all environmental stimuli is perceived as relevant when it contains a specific meaning according to previous experience. Any of these stimuli may potentially contain relevant environmental information, but its relevance arises when it is properly interpreted. The contrast between the present stimuli and previous experience allows predictions to be made about the real presence or absence of danger and selecting the correct coping response [34; 63]. An intriguing aspect is that most studies of the neural and behavioral framework of these types of motor responses have been performed in laboratory animals (i.e., animals that were completely naive of predators before the test). However, some studies in naturally free animals have found similar results [19; 90]. The interpretation is that a neural framework adapted by natural selection is able to respond in some effective way, even in the absence of any previous experience. Therefore, the neural framework allows an initial response to any dangerous sit-

uation in the environment, yielding necessarily useful strategies for survival. Choosing the best strategy to cope with such situations depends on experience (i.e., learning).

5. Communication and anxiety

During natural selection and evolution, several organisms have developed strategies that allow different but complementary forms of communication between individuals of the same species. Thus, animal communication includes the emission and reception of signals delivered in the environment, usually following some specific code. Moreover, communication also includes behaviors in the receptor-individual. Success in the detection of cues includes a series of processes that consist of emission of the cue, reception by other individuals, encoding, transmission, and decoding [26].

Notably, special situations, such as emergency situations, involve most of the sensorial systems. A primitive form of communication is body language. In this case, environmental information is detected by the visual system. Insects frequently apparently dance while performing stereotyped movements [33] that apparently carry a message whose meaning is not yet fully understood.

The auditory system is involved in the most complex of these forms of communication. A symbolic language that contains a characteristic syntactic structure is apparently peculiar to the human species [79]. In a more primitive form, nonsyntactic and perhaps only symbolic language is observed in other species [6]. In fact, animal vocalizations are devoid of semantic content (i.e., meaning) but posses some semiotic context that contains symbolic value [16]. The signals generated by animals are used for communication and consist of signs that become messages that are capable of influencing the behavior of other individuals who are also able to respond with species-typical signals by distinguishing its semiotic content. For example, most ultrasonic vocalizations of animals, including rats, are true semiotic signs and represent a useful signal within a communication system [63]. Most of these semiotic signals may represent warning cues that seemingly produce some anxiety responses in other individuals of the same species.

Among the signaling systems, chemical cues that consist of pheromones [48] can cause striking behavioral responses, including anxiety [31; 32], when perceived by other individuals of the group. The opposite is also true. Some pheromones consist of cues that indicate the existence of a safe environment [47; 103] by informing other individuals of the same species about the absence of danger or presence of food. In both cases, an emitting-individual releases substances to the environment that are recognized by the receptor-individual by specific sensory systems located, for example, in the legs and antennae in insects [81] or olfactory sensory system in other organisms, including mammals [58]. Figure 1.

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6. Neuroanatomical modeling of emotions

Emotional memory allows an individual to recognize signs from the environment and compare them with past experience as an element of judgment to efficaciously respond to the environment by choosing the best coping strategy [14]. During the first half of the 20th century, researchers were interested in the brain mechanisms of emotional behavior [57], and the original concept of the "limbic system" was gradually abandoned. Instead, the very simple, initial anatomical concept (i.e., hippocampus, one thalamic nuclei, mammillary bodies, and cingulum) was enriched by the inclusion of other deep temporal lobe structures, such as the amygdaloid complex [57], so-called mesolimbic structures [73], and prefrontal and orbitofrontal cortices [100]. All of these anatomical regions share similar neurotransmission systems, namely serotonin, norepinephrine, dopamine, and γ-aminobutyric acid (GABA), among others.

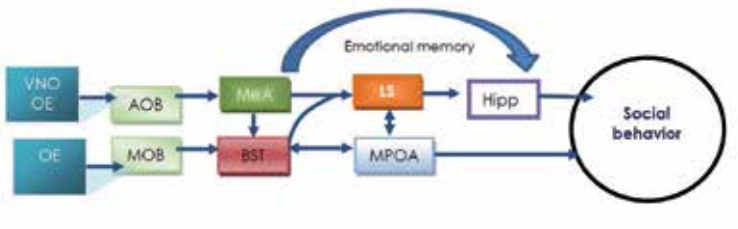

Figure 1. Social recognition and olfactory pathways in rodents. Abbrev. VNO, vomeronasal organ; OE, olfactory epithelium; AOB, accessory olfactory bulb; MOB, main olfactory bulb; MeA, medial amygdala; BST, bed nucleus of the stria terminalis; LS, lateral septal nucleus; MPOA, medial preoptic area; Hipp, hippocampus.

Some alterations in the serotonergic system are associated with psychiatric disorders, such as depression and schizophrenia [87]. Serotonin (5-hydroxytryptamine [5-HT]) is located primarily in the gastrointestinal tract, but it is also detectable in the central nervous system [29] in areas that are functionally related to many behavioral processes. Its main reservoir in the brain is the dorsal raphe nucleus [40; 78], which, among other projections, sends efferent fibers to several structures related to emotional processing, such as the septum, thalamus, amygdaloid complex, nucleus accumbens, hippocampus, and prefrontal cortex [29; 78]. Although a controversial issue [87], an increase of 5-HT in the synaptic cleft exerts anxiolytic effects in animal models of anxiety, such as the social interaction test, light-dark test, Vogel conflict test, Geller-Seifter conflict test, and ultrasonic vocalizations [10, 65], which have been confirmed by many clinical studies [60].

Norepinephrine is related to many functions, such as attention, the regulation of stress, fear, memory, sleep, and wakefulness [27]. It is synthesized in a small group of cells located in the locus coeruleus that sends efferent fibers parallel to those of 5-HT [40; 27]. Norepinephrine is involved in the secretion of corticotrophin-releasing factor, which stimulates the production of adrenocorticotropic hormone that, in turn, releases corticosterone in the adrenal

glands, which is responsible of the metabolic response to stress [100; 67; i.e. an inseparable component of anxiety]. Anxiety is directly related to increased activity of locus coeruleus neurons. Drugs that increase noradrenergic activity also increase anxiety, and drugs that reduce noradrenergic activity reduce anxiety [40, 27]. Limbic and cortical regions innervated by the locus coeruleus are those that are thought to be involved in the elaboration of adaptive responses to stress, such as the typical scheme seen in fearful behavior in cats [1].

γ-Aminobutyric acid is a neurotransmitter distributed throughout the central nervous system and the quintessential inhibitory neurotransmitter [72]. Modulation of the GABAergic system at its receptors [5] is linked to the neurobiological mechanisms that regulate anxiety [72; 70; 86]. Most drugs with affinity for the $GABA_A$ receptor produce anxiolysis and sedation [96]. These receptors are detectable in the cerebral cortex, amygdala, hippocampus, and striatum [40], providing the physiological basis for the therapeutic action of anxiolytics [72], including gonadal steroids and neurosteroids [25; 12; 61].

Mesolimbic dopamine is found in the ventral tegmental area and involved in the control of cognition and affect [46]. Dopamine innervation of the medial prefrontal cortex appears to be particularly involved in mild and brief stress processing [21]. In turn, the prefrontal cortex plays a role in working memory, in addition to other brain areas, such as the hippocampus. A critical range of dopamine turnover is necessary to keep the working memory system active and ready for optimal cognitive functioning [42], a situation that is impaired in situations of extreme stress [3]. In summary, the dopamine system is important for general emotional responses, selective information processing, hedonic impact, and reward learning. In a broader sense, dopamine is important for reactivity to perturbations in the environment, which is essential for the ability (or failure) to cope with the environment [73; 99].

Multiple neurotransmission systems participate in the processing of anxiety and coping with the environment. Many other neurotransmitters are involved in the regulation of anxiety, including neuropeptides [91], polypeptides [95], and amino acids [104]. Nonetheless, a common denominator is that almost all of these neurotransmitters are located within the anatomical substrate of emotional memory [99], namely the amygdala complex [83].

The amygdala is composed of many functionally heterogeneous nuclei [56]. The lateral and central nuclei of the amygdala mediate the acquisition and expression of reactive defensive behaviors [59; 69], and the basal nucleus plays a key role in fear expression [38]. The basal amygdala nucleus, together with the lateral nucleus and accessory basal nucleus, integrate the basolateral amygdala [84]. As a whole, an increase in the neuronal firing rate of the basolateral amygdala has been related to fear [76], anxiety [101], emotional learning [17], and Pavlovian conditioning [28]. The basal amygdala nucleus appears to mediate fear-motivated reactions [55] but not conditioned auditory fear responses, such as freezing [69]. The central nucleus of the amygdala projects to various brain structures via the stria terminalis and ventral amygdalofugal pathway. The anatomical circuit responsible for the startle reflex begins in auditory pathways and reaches the central amygdala nucleus [18]. Pathways from the amygdala to lateral hypothalamus are related to peripheral sympathetic responses to stress [45]. Early findings reported that electrical stimulation of the amygdala in cats produced peripheral signs of autonomic hyperactivity and fear-related behavior, commonly seen when

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the animal attacks or is being attacked [39]. Electrical stimulation of the amygdala in human subjects also produces signs and symptoms of fear and anxiety, namely increased heart rate, blood pressure, and muscle tension, accompanied by subjective sensations of fear and anxiety [9] and an increase in plasma catecholamines [30]. Important reciprocal connections also exist between cortical association areas, the thalamus, and the amygdala, which may account for fear responses [82]. These findings demonstrate that the amygdala plays an important role in conditioned fear and the modulation of peripheral stress responses.

7. Fear and anxiety as a consequence of natural selection

The relationship between mother and child is essential for the survival and normal development of infants [71; 85]. Maternal odors attract and guide neonates to the maternal breast [98]. The role of mothers is to provide a source of nutrition for their offspring, but also to protect them from predators [80; 71]. Maternal odors produce signs of calm. Kittens, pups, and human babies exhibit increased agitation and vocalizations when placed in an unfamiliar environment, but when they return to their nest or stay in close proximity to their mother, they calm down [66; 85]. Amniotic fluid olfaction reduces crying in human babies when they are separated from their mothers [97]. Recently, we analyzed human amniotic fluid, colostrum, and breast milk. Eight fatty acids were consistently found in measurable amounts in these three biological fluids. Both amniotic fluid and a mixture of its fatty acids acted as feeding cues, leading to appetitive behavior [11]. Moreover, both amniotic fluid and a mixture of its fatty acids exerted anxiolytic effects in animal models of anxiety [13]. These findings indicate that a system of protection against anxiety is present during intrauterine life, at least in mammals, suggesting a process of natural selection in which an individual is protected from extreme anxiety, even before birth.

With regard to the opposite process, alarm cues (i.e., pheromones) are released by an animal in threatening situations, informing members of the same species about the presence of danger (e.g., the proximity of a predator; 36). The responses of conspecifics to alarm pheromones include fear, autonomic responses, and freezing [51], increased awareness [35], defensive behavior [52], and an increase in anxiety-like behavior (32; 44; i.e., some behaviors mediated by deep temporal lobe structures). A single exposure to predator odors (i.e., 2,3,5-trimethyl-3-tiazoline) contained in fox feces and cats increased c-*fos* expression in the lateral septal nucleus and central amygdala [19; 90], among other structures. An arterial spin labeling-based functional magnetic resonance imaging study found that neuronal activity increased in the dorsal periaqueductal gray, superior colliculus, and medial thalamus during alarm pheromone exposure [50]. Exposure to odors from potential predators also elicited fast waves in the dentate gyrus [37] and enhanced long-term potentiation in the dentate gyrus [23]. Both the main and accessory olfactory systems are responsive to 2-heptanone [102]. The medial amygdala nucleus receives indirect inputs from the main olfactory system from the piriform cortex, periamygdaloid cortex, and cortical amygdala nucleus and direct inputs from the accessory olfactory system [92]. The hippocampus also receives odor information from both olfactory systems through entorhinal cortex connections [77]. Herein, neurons

from medial and cortical amygdala nuclei are activated in the presence of alarm pheromones [52], and the medial amygdala is involved in the neuronal circuitry associated with memory formation related to odors derived from predators, further leading to the expression of unconditioned and conditioned fear behavior [68; 93]. Figure 2.

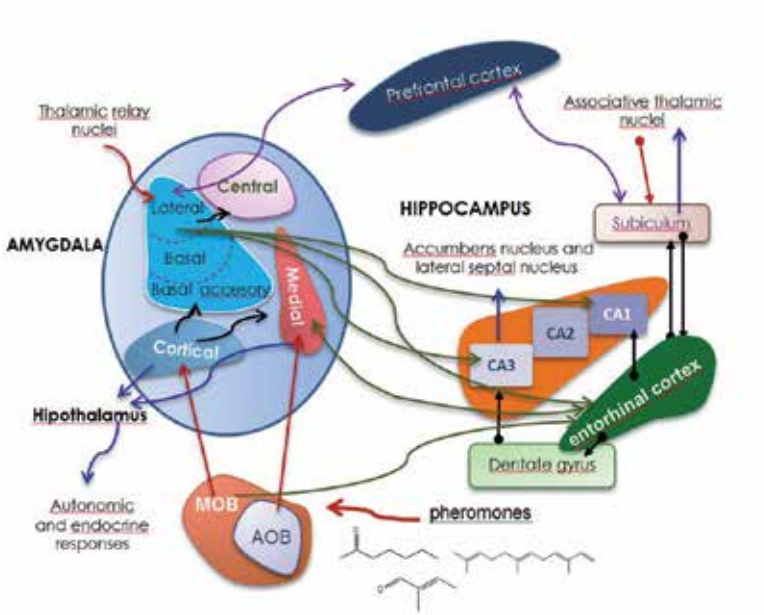

Figure 2. Anatomical representation of emotional memory circuit. Connections between amygdala and hippocampus, modulate the use of memories related to sensorial stimuli. Abbrev.: AOB, accessory olfactory bulb, MOB, main olfactory bulb.

8. Conclusions

Most of the known responses to alarm cues have come from studies in laboratory animals that reproduce and feed under relatively comfortable conditions. They live inside very well controlled facilities, distant from predators and dangerous situations. One may reconsider the concept of the rhinencephalon, an almost forgotten anatomical entity that involves brain structures (Figure 3) related to emotional memory and is present in mammals, reptiles, and birds. The rhinencephalon, at least as a concept, contains one of the primitive sources of capturing information from the environment—the olfactory system. The concept is completed by connections of this sensorial system with deep temporal lobe structures (i.e., emotional memory-related structures). Therefore, the existence of the rhinencephalon in many species suggests that the integration of anxiety responses is a broad, essential characteristic determined by natural selection. In such a case, anxiety as an adaptive response is common to species with a centralized nervous system. Anxiety as an adaptive response is also naturally

contained in the brain, and it is expressed even before the organism learns the most efficacious behavioral response.

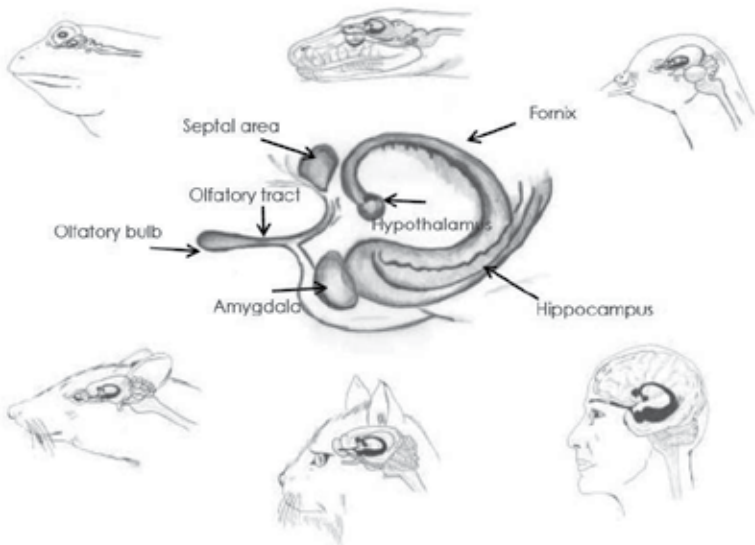

Figure 3. Squematic representation of rhinencephalon in several species. Since on evolution point of view (shaded area), rhinencephalon represents as integrative and primitive framework present in the central nervous system, integrating emotions escential for survivance, such as fear and anxiety.

Nature protects the mother and fetus during intrauterine development, in which the development of the fetus occurs in an environment that protects it from anxiety. Especially in mammals, early learning acquired through maternal-infant interactions during the first phase of life and subsequent learning acquired through interactions with dominant members of a given group allow the individual to learn to select the most effective survival strategy, with the participation of prefrontal brain structures.

Consequently, two processes occur. One process depends on the neural framework that will respond even in the absence of any previous experience. The other process is a consequence of learning. Working together, the outcome is the utility of anxiety as an adaptive reaction that contributes to the survival of the species.

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Section 2

Basic Research

Chapter 3

Focusing on the Possible Role of the Cerebellum in Anxiety Disorders

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Additional information is available at the end of the chapter

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1. Introduction

The cerebellum is traditionally thought of as the neural structure responsible for motor control, voluntary movement, balance and associative learning. However, there is a growing awareness that the cerebellum plays a role in higher cognitive functions such as sensory processing [1,2], attention [3,4], verbal working memory [5-8] and emotion [9-11]. Converging evidence suggests that the cerebellum may play a role in anxiety disorders. With the greater appreciation that anxiety disorders are best conceptualized by diathesis models of risk, cerebellar activation may represent an endophenotype contributing to anxiety etiology.

This chapter will present the role of a normal functioning cerebellum and outline instances in which abnormal functioning underlies a variety of pathologies including anxiety disorders. We will begin by describing historically accepted roles of the cerebellum in motor control, timing, and learning and memory. We will then present research relating to less appreciated roles such as executive processing and emotional control to demonstrate less recognized cognitive and emotional capacities of the cerebellum.

Key to our theory is that individual differences in cerebellar activity underlie vulnerability to develop anxiety disorders. This argument will be presented by providing an overview of pre-existing vulnerabilities contributing to a diathesis approach of anxiety. We will discuss recent research in which individual differences in cerebellar modulated activities is present, such as during associative learning, avoidance or image processing tasks. Finally, a diathesis model which incorporates cerebellar activation into the etiology and expression of anxiety disorders will be presented with a discussion of its implications and future directions.

2. Historically accepted roles of the cerebellum

The cerebellum is a unique neural structure that accounts for approximately 10% of the total brain volume and contains nearly half of all the neurons of the brain [12,13]. The cerebellum is highly organized, with distinct inputs and outputs. It is made up of an outer region of gray matter (the cerebellar cortex), an inner region of white matter, and three pairs of deep nuclei responsible for cerebellar output; the dentate, the fastigial, and the interposed[13]. The cerebellum is made up of two hemispheres that are structural mirror images, each containing three deep nuclei. The two hemispheres are connected medially by the vermis. For specificity, the cerebellum is segregated into sections: Crus I, Crus II, and lobules I-X ([14].

Motor Functioning. The traditional view of the cerebellum is that of a motor comparator. Muscle movement, especially coordinated and smooth motions, are the product of a feedback loop involving the cerebellum and frontal cortex. Afferent connections via the cortico-pontine-cerebellar tract with the premotor and motor cortex carry a "copy" of motor demands to the cerebellum. The cerebellum then compares feedback from the muscle spindles, joints, and tendons via the cerebellar peduncles to modify motor behavior, maintain coordination and perform skilled movements [15-17].

The essential role of the cerebellum in motor behavior is especially evident following cerebellar insult. Unlike lesions of the motor cortex, a cerebellar lesion does not eliminate movement entirely. Instead, it disrupts initiation, coordination, and timing of movements. Movement deficits following cerebellar lesions can be very precise. Some lesions affect certain muscle groups, but not others, depending on the location, revealing a precise topography in the cerebellum. For example, deterioration of the anterior cerebellum affects the lower limbs, causing a wide staggering gait, while largely sparing arm and hand movements [18-21]. Cerebellar lesions often lead to a lack of coordination, affecting the ability to perform directed movements. Damage to the vestibulocerebellum, which receives input from the vestibular nuclei, affects gross movements, such as standing upright, to fine movements, such as maintaining fixation of gaze. Spinocerebellar lesions disrupt signals from the spinal cord and affect coordination interfering with movement regulation. The spinocerebellum uses a feed-forward process to make on-line updates to ensure accurate coordinated movements. Lesions of the cerebellum cause a variety of movement disorders such as overshooting or undershooting of targets (referred to as dysmetria), poor path correction caused by poorly coordinated joint motions (known as ataxia), tremors at the end of actions [13,18,22]. Finally, insult of the cerebrocerebellum, which has afferents from the cerebral cortex, impairs planned movements and sensory input, affecting reaction time. Individuals with lesions to the cerebrocerebellum report difficulty performing directed actions. Instead of a smooth integration of movements toward a target, their actions take place as a series of several movements strung together, known as decomposition of movement [18]. Altogether, the profound and specific outcomes of cerebellar insult indicate its critical role in coordinated motor behavior, enabling smooth and accurate performance of highly specific fine motor movements.

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Timing. Given its role in motor behaviors outlined above, it is not surprising that the cerebellum is essential in motor timing, which produces timed movements by coordinating velocity, acceleration and deceleration [15,23-28]. A simple way of measuring motor timing is through repetitive finger tapping tasks. Participants are asked to tap in time with a pacing device (e.g., metronome). After synchronization, the training device is removed and the individual is asked to continue tapping at the same interval. Variability in timing can then be measured in the inter-tap intervals. This simple task elucidates the essential role of the cerebellum in motor timing. Healthy participants demonstrate a significant increase in cerebellar activity (in addition to other areas related to motor timing such as the supplementary motor area and basal ganglia) during timed finger tapping [28]. Patients with lateral cerebellar lesions demonstrate increased variability when performing rhythmic tapping with the affected (ipsilateral) finger, but not when tapping with the unaffected (contralateral) finger. Interestingly, those with medial cerebellar lesions did not show timing errors, but had a greater number of motor errors, supporting involvement of the cerebellum specifically in timing and not just in producing the behavioral motor output [23].

Timing is also essential in higher cognitive functions such as stimulus processing, expectations, language, and attention. Sensory timing is often measured by duration judgment tasks, which presents two stimuli of either the same or different duration. Here, participants are required to attend to a stimulus, maintain it in working memory, compare it to a second stimulus and make a judgment. Significant increases in cerebellar activity are present during timing tasks in healthy human participants [29,30]. Additionally, the use of repetitive transcranial magnetic stimulation (rTMS), which induces inhibition and causes a "temporary lesion" in the stimulated region, of the lateral cerebellum impaired short interval time perception in a similar task (400-600 ms) [31]. Comparable sensory timing deficits are seen in children with Ataxia Telangiectasia, a disease involving cortical degeneration affecting Purkinje and granular cell layers [32]. A similar deficit in duration judgment is seen in patients with cerebellar tumors [33]. Furthermore, the effect of cerebellar lesions on sensory timing is not specific to duration judgment tasks. Patients with cerebellar lesions display deficits in a variety of other tasks requiring sensory processing including interval discrimination [24,34], speed judgments [35,36] and verbal timing [37-41].

Eyeblink conditioning. Although the cerebellum has long been acknowledged as a motor integrator and modulator, associative learning was assumed to be accomplished by higher cortical regions. Over the latter quarter of the 20th century, Thompson and colleagues presented a body of work that the cerebellum is part of the intrinsic circuitry for eyeblink conditioning, a form of new motor learning [42-45]. The foundation of eyeblink conditioning is the simple reflex pathway; the unconditional stimulus (US) produces an unconditional response (UR). Introduction of a second stimulus (conditioned stimulus or CS) that is temporally paired with the US gives rise to a conditioned response (CR), which precedes or significantly modifies the UR. In delay conditioning, the CS precedes and coterminates with the US. Thompson recognized that the simplicity of eyeblink conditioning coupled with the ability to explicitly assess reactivity to the CS, to the US, or its combination under various

conditions provided an excellent platform to understand the nature of the engram – the storage and location of a memory trace [42,46,47].

The intrinsic cerebellar circuitry demonstrates why damage to the cerebellar cortex, cerebellar nuclei, or major afferent pathways abolishes or impairs acquisition of the CR during eyeblink conditioning [48-53]. Using rats and rabbits, the neurobiology of eyeblink conditioning has been reduced to two pathways that converge in the cerebellum (For detailed reviews see [45,54]). The basic essential pathway is presented in Figure 1. Simplified, the CS pathway transmits auditory, visual, and somatosensory information via the pontine nuclei to the cerebellar cortex and interpositus nucleus via mossy fiber connections. The US pathway takes two routes from the trigeminal nucleus: a reflexive route that bypasses the cerebellum and a learning route that integrates the relationship between the CS and US. From there, climbing fibers synapse at the cerebellar cortex and interpositus nucleus. The CS and US pathways converge in the cerebellar cortex and anterior interpositus. It is here where the memory trace is stored by changes in the firing patterns of purkinje cells during the development of the CR [47,55-57]. The CR is produced by release of inhibition of the interpositus, which increases activity to the red nucleus, in turn causing the cranial motor nuclei to induce an eye blink response [58,59].

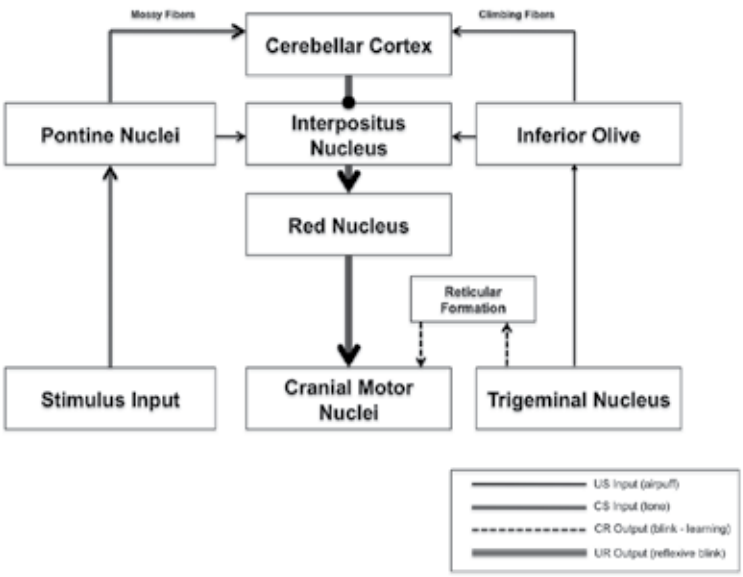

Figure 1. Intrinsic delay eyeblink conditioning pathway. Adapted from Christian & Thompson, 2003.

Another benefit of the eyeblink conditioning paradigm is that the same parameters can be used across animal species, in humans, and even in early infancy. Consistent with the animal literature, intact cerebellar structures are necessary for the acquisition of the CR in eye-

blink conditioning in humans [48-50,60]. Furthermore, imaging studies indicate that activity in the cerebellum is significantly greater during eyeblink conditioning in humans [61-65].

Given the advanced understanding of neurosubstrates and its amenability for cross species comparisons, eyeblink conditioning has been a platform for understanding clinical abnormalities and cerebellar dysfunction. Therefore, a more detailed review will be presented for eyeblink conditioning, as well as a selection of clinical examples in which a cerebellar role is revealed by eyeblink conditioning.

Cerebellar abnormalities and eyeblink conditioning. The cerebellum is particularly affected by ethanol alcohol, with alcohol-related diseases causing serious damage to its development and cells. For example, impaired delay eyeblink conditioning has been observed in Korsakoff patients, recovered alcoholics, and children with Fetal Alcohol Syndrome [66-69]. However, not all disorders cause deficits in eyeblink conditioning. For example, individuals with autism acquire eyeblink conditioning faster than matched controls, although the form of the CR is altered [70,71]. Schizophrenia also alters cerebellar functioning, with facilitated eyeblink conditioning observed in schizophrenics compared to healthy controls [72]. Some interventions can also rescue or improve cerebellar functioning. For example, improved performance in eyeblink conditioning has been observed in mice following an antioxidant rich diet over a standard diet [73].

Regardless of etiology, cerebellar abnormalities affect eyeblink conditioning. The well-documented pathways, substrates, and lesion studies makes eyeblink conditioning a simple, yet sensitive tool to understand the cerebellar role in various neuropathologies.

3. Higher cognitive and emotional capacities

Recently, the cerebellum has garnered greater attention for its higher cognitive capabilities. Reviews such as those from Courchesne and colleagues [3,74], Schmahmann and colleagues [75,76] and others [77-79] establish the cognitive role of the cerebellum, which will be briefly summarized here.

Anatomy. In order to have a role in higher cognitive processing the cerebellum must maintain connections with neural structures known to influence cognition. As such, cerebellar efferents have been traced to both motor and non-motor areas of the frontal cortex [80-85]. Tract-tracing studies with primates indicate that cerebellar output to the dorsolateral prefrontal cortex (DLPFC) places it in a position to modulate higher cognitive processing. Transneuronal retrograde virus tracers injected into multiple areas of the DLPFC (Brodmann areas 9, 46 and 12) labeled neurons in the dentate nucleus, indicating that the dentate has output channels to prefrontal regions [84]. The DLPFC plays an important role in many aspects of executive functioning including organization [86,87], behavioral control [87] working memory [88,89], reasoning and decision making [90], reward and expectancy [91], and emotion and motivation [92]. Follow up studies were able to pinpoint lateral dentate projections to the prefrontal cortex (PFC), with separate dorsal dentate projections terminat-

ing in the motor and premotor regions, suggesting a topographic organization of the dentate nucleus with both motor and non-motor output to the cortex [93].

Functional connectivity. Cerebellar connectivity to non-motor cognitive areas in human imaging research reflects pathways implicated in primate studies. Functional connectivity MRI correlates signal fluctuations in one brain area with activity in another, implying a relationship between the two areas. Using this method, Allen et al. [94] found that activity in the dentate nucleus of the cerebellum correlated with changes in activity in non-motor regions such as the limbic system, parietal lobes, and prefrontal cortex. Connectivity between the cerebellum and anterior cingulate cortex, a region typically associated with error detection, anticipation, attention, and emotional responses, has also been reported in resting state paradigms [95]. Furthermore, there is evidence that the cerebellum contributes to the intrinsic connectivity networks, a series of brain structures that correspond to basic functions such as vision, audition, language, episodic memory, executive functioning, and salience detection [11]. Distinct contributions of the neocerebellum to the default mode network, the executive network, and the salience network substantiate the assertion that there is functional connectivity between the cerebellum and non-motor cognitive regions.

Clinical support for a cerebellar role in non-motor cognitive processes is established by the work of Schmahmann and colleagues. Schmahmann recognized that not all patients with cerebellar strokes present with motor deficits. By assessing motor impairments alongside stroke location, he found that individuals with posterior lobe lesions presented with minor if at any motor impairments. Instead, they suffered from behavioral changes affecting executive functioning, verbal fluency, working memory, abstract reasoning, spatial memory, personality, and language deficits; recently coined as *cerebellar cognitive affective syndrome* [96,97].

Loss of function in lesions is supported by activational studies in healthy humans. Using functional MRI, significant changes in cerebellar activity is present during tasks that are considered largely cognitive or to involve executive processing. Significant increases in cerebellar activity have been recorded during sensory timing [29,30], spatial attention [98-101], and verbal working memory tasks [5,6,102].

Anatomical and functional connectivity, specific activation during executive processing tasks, and impairments concomitant with lesions is convincing evidence that the cerebellum plays a critical role in higher cognitive processing.

Emotions. In addition to connections with prefrontal and frontal cortex, the cerebellum also has direct anatomical connections to the amygdala, the brain region typically associated with emotion and fear [103]. Functional support for this connectivity comes from imaging studies that demonstrate judging emotional intonation, feeling empathy, experiencing sadness, and viewing emotional pictures all correlate with increased activity in the cerebellum [9,76,104-106].

If the cerebellum has important connections to the limbic system, then it follows that stimulation of the cerebellum should result in changes of emotional behaviors. As such, electrical stimulation of the cerebellum in animals demonstrates that it is an important modulator of

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behaviors classically attributed to limbic functioning including grooming, eating, and sham rage [107-109]. Bernston et al. [107] reported that stimulating the cerebellum of cats induced grooming and eating behaviors, in addition to similar findings with rats [108,109]. The cerebellum, specifically the vermis, plays a role in fear and avoidant behaviors. For example, lesioning the vermis alters fear responses by decreasing freezing and increasing open field exploration [110]. On other other hand, stimulating the vermis induces fear responses, such as increased amplitude of the acoustic startle response [111], indicating cerebellar modulation of species-specific behaviors beyond coordination of muscle movements.

Reports from the clinical literature also support cerebellar modulation of emotion. Attempts to treat severe seizure disorders by stimulating the cerebellum provide unique case reports of observations about cerebellar functioning. Heath et al. [112] placed electrodes in the fastigial nucleus of an emotionally disturbed patient and observed increased activity in the region when the patient reported being angry or fearful. Descriptions of unpleasant sensations and the feeling of being scared were reported following stimulation of the dentate nucleus [113]. In a larger study of cerebellar stimulation as a treatment for chronic epilepsy, Cooper et al. [114] reported marked behavioral changes from sullen mood, dangerous, and aggressive behaviors to open, pleasant, responsive, and sociable affect in patients. More recently, descriptions of highly specific lesions to the cerebellar vermis includes personality changes, especially emotional effects such as flattening of affect [97,115]. Observations from these case studies suggest that the cerebellum may utilize its reciprocal connections with the prefrontal cortex and limbic system to modulate emotional processing.

Cerebellum and Anxiety Disorders

Anxiety. Anxiety is the most prevalent disorder in the United States with one quarter of the population estimated to develop an anxiety disorder at some time in their lives [116,117]. On the other hand, three quarters of the population does not suffer from clinical anxiety, raising the question what is it about an individual that makes them more likely to develop an anxiety disorder? Unfortunately, there is no single vulnerability increasing risk for anxiety. Instead, anxiety disorders are best represented by diathesis models, that is, preexisting conditions enhance risk such that individuals are vulnerable to environmental insults or challenges. A stress-diathesis model for anxiety disorders emphasizes changes in stress reactivity from the convergence of a variety of factors such as genetics, biology, sex, and prior experience [118]. Current research efforts heavily focus on the higher cortical areas (e.g., prefrontal cortex, cingulate cortex, hippocampus, amygdala) as areas critical to development of anxiety. However, the cerebellum is also intimately involved in emotional processing, learning and memory – all of which are represented as risk factors in diathesis models. The following sections will describe how cerebellar activity is related to the signs and symptoms of anxiety and provide often overlooked evidence of cerebellar involvement from imaging research. This will form the basis for speculations regarding individual differences in cerebellar activity as a risk factor for anxiety disorders.

Avoidance. Avoidance is the core feature in the otherwise varied symptomology of anxiety disorders [119]. Therefore, it is essential to understand the role abnormal expressions of avoidance plays in the development and maintenance of anxiety. First, avoidance is ac-

quired and reinforced over time. The essence of anxiety is concern over a potential threatening event in the future, typically one which the individual feels they have no control over and could not cope with. Rather than deal with uncontrollable events, anxious individuals choose to exert their control by substituting other negative thoughts or feelings that are avoidable, providing short term relief and a feeling of temporary control. Avoidance can either be active or passive. In active avoidance, the individual learns to control their environment by alleviating or removing a noxious stimulus. In passive avoidance, the individual learns not to place themselves in a situation that previously contained a noxious stimulus. In anxiety, both forms of avoidance are present, and over time, become pervasive and uncontrollable such that normal functioning becomes impossible.

Avoidance is a learned process. Therefore, it is possible to measure the differences in acquisition of the negative reinforcement learning seen in active-avoidance. Differences in the speed and strength of acquisition in active-avoidance may contribute to risk or resiliency. Some individuals may be more susceptible to acquire and repeatedly express active-avoidance behaviors, leading to development of behavioral and cognitive avoidance symptoms associated with anxiety disorders.

Although the cerebellum is typically associated with associative learning using classical conditioning protocols, a cerebellar role in operant learning such as avoidance has also been suggested. For example, lever press avoidance paradigms places a rat in an operant chamber and presents a stimulus (e.g., tone) that precedes and overlaps with an aversive stimulus (e.g., a shock). Over time, the rat learns to make a lever press response to the tone, avoiding the shock. Lesioning the cerebellum prevents acquisition of the avoidance response in this task [120] and in other measures of active-avoidance [121]. Furthermore, cerebellar involvement may play a role in human avoidance as well [122].

Neuropharmacology. Given the role of the cerebellum and associative learning in anxiety vulnerability, it would be useful to consider treatment approaches that target the cerebellum. Among others, the cerebellum maintains a large density of corticotrophin-releasing hormone (CRH) receptors and cannabinoid receptors. Here, we will outline how these receptors relate to anxiety and eyeblink conditioning.

The influence of CRH on various behavioral markers of anxiety demonstrates its role in modulating stress reactivity. CRH has anxiogenic properties, with a dysregulation of CRH systems playing a role in anxiety disorders. The cerebellum contains a high density of CRH1 receptors, the receptor linked to stress responding, anxious behavior and cognitive functioning [123]. The effects of CRH receptor activation have been thoroughly outlined using animal models, including its influence on anxiety (for a review see [124]). For example, an injection of corticotropin releasing factor (CRF), which induces corticosterone release (the animal analog of cortisol), has been shown to decrease open field exploration, time spent in open arms in the elevated plus maze, exploration in novel environments, and social interaction in rats at certain doses. Furthermore, injections of CRF increase startle amplitude, and improve acquisition in both active and passive avoidance paradigms. Additionally, CRH receptors are adaptive to environmental demands, with a variety of stressors upregulating CRH1 receptors specifically, suggesting a relationship to chronic stress that may feed for-

ward into anxiety disorders [125,126]. Eyeblink conditioning is also influenced by CRH, with studies demonstrating facilitated acquisition in trace paradigms of both humans and rats [127-129]. Humans treated with metyrapone, which decreases initial cortisol response to stress (although not long term effects of stress [130], acquired trace eyeblink conditioning faster than placebo treated controls. While there were no acquisition differences between the groups in delay-type conditioning, metyrapone treated individuals were significantly slower to extinguish, a difference not seen in the trace group [128]. Altogether, it appears that stress reactivity in the brain impacts cerebellar functioning and may play a role in modulating learning and memory, feeding into anxious behavior and increased vulnerability to anxiety disorders.

Cannabinoid receptors, which have their highest densities in the frontal cortex and cerebellum, have also been linked to anxiety [131-133]. Low doses of cannabinoid compounds induce anxiolitic effects, with high doses causing anxiety-like reactions in laboratory rats, suggesting interplay between cannabinoid receptor activity and anxiety [134-136]. These findings are in conjunction with subjective reports that exposure to cannabis derivatives can induce feelings of placid relaxation or panic [137]. For example, low doses of a cannabinoid synthetic reduces behaviors linked to stress in rats with high doses of the same drug causing the opposite pattern, inducing anxiety to novelty and increasing corticosterone [135]. Aside from synthetic activation, endogenous cannabinoid receptor activity is related to anxiety as well. Pharmacological blockage of the CB1 cannabinoid receptor increased anxiety-like behaviors in rats including reduced open arm exploration in the elevated plus maze and increased withdrawal-related behaviors [132]. Cannabinoids influence anxiety and have a high density of receptors in the cerebellum, suggesting that cannabinoid receptor activation would influence eyeblink conditioning as well. As such, animal models have demonstrated that CB1 knockout mice demonstrate disrupted eyeblink conditioning [138] In conjunction, humans who report chronic cannabis use (but not at the time of the study) exhibit fewer and poorly timed CRs during delay eyeblink conditioning compared to non-users [139].

Temperament differences contributes to anxiety vulnerability

Diathesis models suggest that the interplay between risk factors increases vulnerability to develop anxiety disorders. Personality is among the many risk factors suggested to play a role in anxiety, with certain personality types at increased risk to develop anxiety disorders. Support for a personality risk factor in anxiety is supported by the low success rates in treating anxiety disorders, which would require the alteration of stable character traits. Of the few studies that have assessed long-term treatment outcomes of anxiety disorders, 30%-50% still have moderate to severe anxiety six years post treatment [140,141].

An understanding of how personality interacts with anxiety is essential. Here, we will discuss an innate feature of personality known as temperament. Temperament is a core feature of personality, often evident early in childhood and remains stable throughout the lifespan. By measuring temperaments related to anxiety such as behavioral inhibition (BI) and trait anxiety, we are able to differentiate at-risk individuals and assess individual differences on cerebellar modulated tasks.

Behavioral inhibition. Similar to anxiety disorders, a core feature of behavioral inhibition is avoidance. Additionally, the behavioral and physiological functioning of an individual with behavioral inhibition is comparable to that seen in anxiety including withdrawal, apprehension, and slow latency to approach unfamiliar people or objects [142]. Kagan and colleagues have provided an extensive behavioral profile of BI using longitudinal methods, reporting that children classified as inhibited at 21-months demonstrate avoidance of social interactions [143], reported more phobias, and had a higher incidence of anxiety disorders [144-147]. As with anxiety disorders, it appears that inhibited temperament is a heritable trait [148]. Parents and siblings of those children classified as inhibited were more likely to have anxiety disorders, social phobia, avoidant and overanxious disorders compared to the families of uninhibited children [149-151].

So far, we have provided evidence supporting that cerebellar differences underlie higher cognitive processes including anxiety disorders. We have outlined the essential role avoidance has in the development and maintenance of anxiety disorders and how learning processes may underlie increased avoidance. We then introduced behaviorally inhibited temperament, a risk factor with many similarities to anxiety. In the next section we will combine individual differences in cerebellar functioning, avoidance, learning, and temperament to provide a cerebellar diathesis theory of anxiety vulnerability.

As described above, avoidance in the development of anxiety disorders is a feed-forward process, such that the expression of avoidance reduces stress in the present while simultaneously increasing the aversiveness of the undesired stimulus or state in the future, increasing the likelihood of continued avoidance behaviors. Both adaptive and pathological avoidance can be described in terms of the degree and rigidity of expression, the sensitivity to acquire stimulus to stimulus associations, and inflexibility to change. Multiple processes underlie avoidance acquisition, making it difficult to tease out the essential factors in anxiety. It is possible that increased sensitivity to the cues and contingencies in the environment are learned faster in anxiety, resulting in better performance on avoidance tasks. One way to measure these associations is through the classically conditioned eyeblink response. The use of eyeblink conditioning allows multiple measures to be taken into account including reactivity, acquisition of the relationship between the CS and US, and rate of extinction.

Learning. The inbred Wistar-Kyoto rat (WKY) provides a model of inherent anxiousness and vulnerability to stress, similar to what is seen in a behaviorally inhibited personality profile [152-160]. Furthermore, the WKY demonstrates enhanced active avoidance in lever-press paradigms, reinforcing the relationship between anxiety vulnerability and avoidance [161,162]. Comparisons of WKY male rats to outbred Sprague-Dawley male rats demonstrate significantly faster acquisition and greater asymptotic performance of the WKY [163,164]. Moreover, avoidance perseverates in WKY during extinction training in the presence of safety signals [159] or avoidance acquisition with more intense stressors [165]. As reviewed by Jiao [166], the WKY provides an animal model of inhibited temperament, faster associative learning, enhanced sensitivity to acquire avoidance, and resistance to extinction. Moreover, the reactivity increases in the face of avoidance acquisition, reminiscent of increased reactivity in PTSD [167].

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Striking parallels are evident between rat models of anxiety vulnerable temperament and humans with self-reported inhibited temperament, suggesting a common neural substrate. One way to assess at-risk temperament is through self-report scales such as those that measure behavioral inhibition [168,169] or trait anxiety [170]. Using these measures, our lab has found that at-risk individuals acquire the relationship between the CS and US the faster, demonstrating more CRs earlier in the training period than those who are low scoring [171,172]. For example, a recent study with a large sample of 117 healthy college-age students found that those scoring high on the Adult Measure of Behavioural Inhibition [169] and Trait Anxiety [170] acquired standard delay eyeblink conditioning faster than those who scored below the median on these measures (see Figure 2). Considering the intimate relationship between associative learning of cues as predictors of aversive events, enhanced classical conditioning may reflect increased sensivity to acquire avoidance responses.

These and other similar results [171,173,174] suggest that individual differences in acquisition of learning tasks may reflect processes underlying increased risk for anxiety disorders.

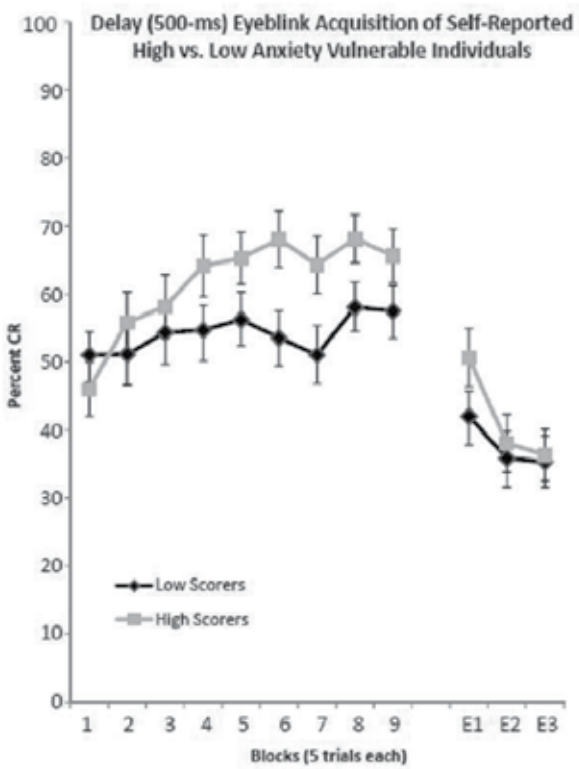

Figure 2. A comparison of temperament on delay eyeblink acquisition of healthy college-aged students. Those who score above the median on the AMBI and STAI-Trait are considered high scorers, those below are considered low scorers Anxiety vulnerable individuals acquired eyeblink conditioning faster and to a greater degree over the 45 trial training period (blocks 1-9). There were no observed differences in extinction (E1-E3).

Heart Rate. In addition to higher cortical pathways, the cerebellum also has direct reciprocal connections to the hypothalamus. Studies in rats and primates show projections from the deep cerebellar nuclei to the lateral hypothalamus, posterior hypothalamic area, dorsal hypothalamic area, the paraventricular nucleus, and the dorsomedial hypothalamic nucleus (For a review see [175]), some of which may be related to heart rate reactivity.

Research in behaviorally inhibited children indicate that a high and stable heart rate (compared to uninhibited children) is indicative of long-term inhibited temperament. Reduced resting heart rate variability has been revealed as a feature of perceived stress [176] and anxiety disorders such as PTSD [177]. The presentation of novel or negative stimuli in healthy populations results in large bradycardic response, with greater bradycardia to more negatively valenced images [178,179]. While there appears to be a relationship between heart rate and anxiety, few studies have looked at heart rate reactivity in behaviorally inhibited adults. Studies that manipulate heart rate typically do so with negatively valenced pictures, assessing reactivity to extreme stimuli (i.e., trauma images for a PTSD patient). In order to disentangle individual reactivity from heart rate changes during high-arousal image processing, which can cause large responses in everyone, a recent study from our lab assessed heart rate change in high and low BI individuals when viewing images that were low in arousal across positive negative and neutral valence. Using this design, we could better understand how BI influences reactivity to everyday stimuli normally encountered in the environment to see if inhibition is related to aberrant parasympathetic or sympathetic activation. Recordings of 6 seconds before, 6 seconds during, and 6 seconds after image presentation suggest a sustained bradycardia in inhibited individuals compared to their non-inhibited counterparts. It is possible that greater vagal tone in high BI could also be related to the enhanced eyeblink acquisition seen in behaviorally inhibited individuals in across studies in Veterans, high school aged students, as well as college aged individuals (See Figure 3).

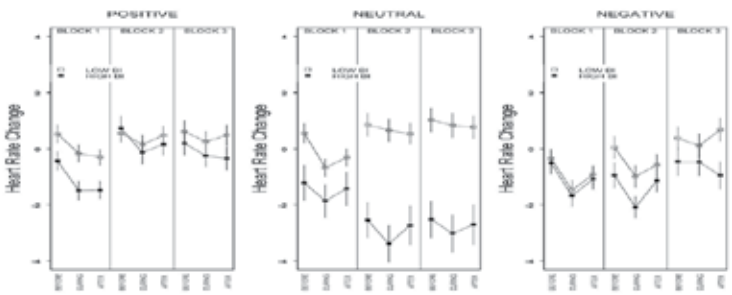

Figure 3. Heart rate change from baseline for positive, neutral, and negative images in high and low behavioral inhibition. Each block represents 20 trials. Behaviorally inhibited individuals showed sutained bradycardia over the neutral picture viewing session. Bradycardia lasted only through the first block of 20 trials in the positive condition, and appeared in the second block (trials 21-40) in the negative condition.

Cerebellar reactivity. Despite being largely ignored and generally not discussed, imaging studies repeatedly indicate significant changes in cerebellar activity of patients with anxiety disorders compared to healthy controls. Close examination of the reported data reveals significant changes in the cerebellum during resting state and anxiety-provoking tasks in social anxiety disorder [180-182], post-traumatic stress disorder [183-187], obsessive compulsive disorder [188] and generalized anxiety disorder [189,190].

Individual differences in cerebellar reactivity have recently been extended to include anxiety vulnerability. Numerous studies assess the correlation between measures of anxiety vulnerability, most often trait anxiety, and brain activity [191]. Mostly, these studies report that individual differences in amygdala and PFC activity underlies trait anxiety, modulating stimulus processing and increasing hypervigilance [192-195]. What is often overlooked is that reciprocal connections between the cerebellum, prefrontal cortex, and amygdala position the cerebellum to modulate reactivity in anxiety vulnerable individuals. In the only published study to date to our knowledge that discusses cerebellar activity and temperament, Blackford and colleagues [10] compared behaviorally inhibited to uninhibited individuals when viewing familiar and novel faces and found significant increases in BOLD activation in the right cerebellum of the inhibited individuals when viewing novel faces. Specifically, they reported significant increases in the right Crus 1/Lobule VI region of the cerebellum, which may be related to processing the valence of emotional cues, salience detection, and in sensory processing and expectation; especially pain-related processes like fear and startle reactions [2,11,76].

The cerebellar differences found in the Blackford study were the result of a full-brain analysis; importantly, standard imaging procedures often incompletely image the cerebellum, so it is possible that the entire structure is not included in typical analyses. Recent research in our lab has explored the relationship of cerebellar activity and anxious temperament as measured by behavioral inhibition and trait anxiety. To extend the Blackford study we again used familiar faces and novel faces. Additionally, we used familiar and novel scenes, allowing us to differentiate the effect of social stimuli and novelty. Furthermore, we used the cerebellum as our region of interest, ensuring complete coverage during imaging. Finally, participants underwent eyeblink conditioning in addition to imaging (outside of the scanner). Given what is known about the behavioral profile of behaviorally inhibited individuals and in light of previous research, we hypothesized that high behavioral inhibition would correlate with changes in cerebellar activity, with the strongest differences occurring to novel faces. We found that the group with higher scores on measures of behavioral inhibition [168,169] had greater cerebellar reactivity to the novel faces compared to baseline than those with lower scores, a difference not seen with familiar faces. Additionally, we observed greater activity of the high BI group when viewing novel scenes, suggesting that the cerebellum may be sensitive to novel stimuli in general. Differences in percent signal change and BOLD signal activations can be seen in figure 4. In eyeblink conditioning, individuals with high BI scores acquired delay eyeblink faster than those with low scores, replicating previous work in our lab.

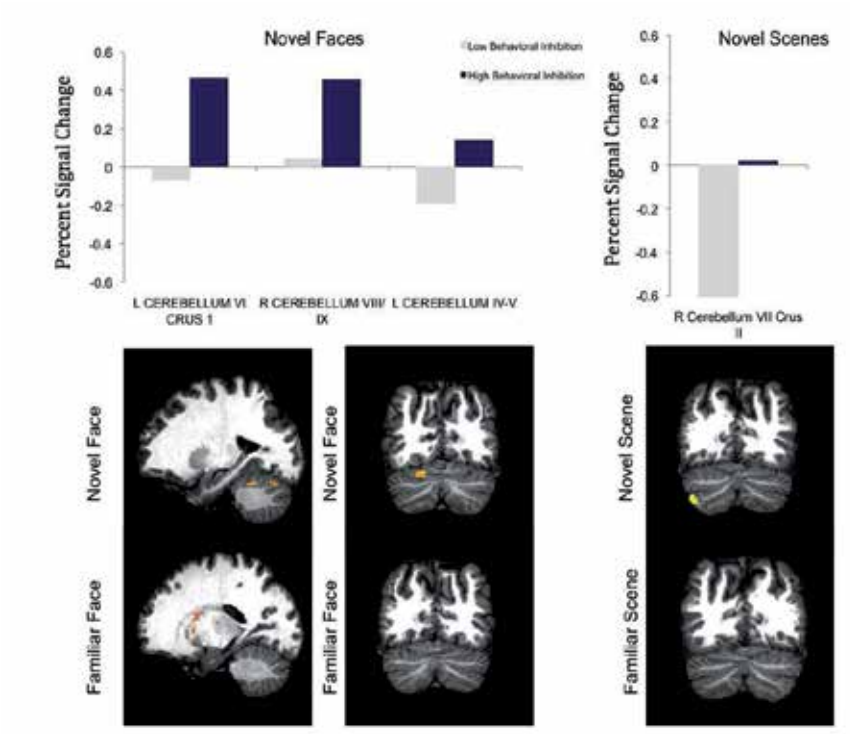

Figure 4. Increased cerebellar reactivity to novel stimuli in anxiety vulnerable individuals. Healthy, college-aged students who scored high on measures of behavioral inhibition demonstrated increased reactivity to multiple areas of the cerebellum in response to novel faces compared to baseline. A similar differential increase in activity was seen for novel scenes. Significant differences in cerebellar activity from baseline were not seen in the familiar face or familiar scene conditions. Left is Right.

We have demonstrated individual differences in cerebellar reactivity and behavior in cerebellar-modulated tasks related to anxiety and anxiety vulnerability. By modulating the signal from higher cortical areas, the cerebellum may be involved in processes related to emotion and anxiety. Figure 5 outlines the cerebrocerebellar and corticopontinecerebellar circuitry as well as the cerebellar outputs for eyeblink conditioning, heart rate responsivity, and higher cognitive process. Cerebellar outputs to prefrontal regions such as the DLPFC and ACC would allow it to modulate incoming signals to these areas regarding higher cognitive functioning including emotion and anxiety. The anatomical pathways, functional connectivity, and individual differences observed of both clinical anxiety and anxiety vulnerable individuals suggest a cerebellar role in anxiety disorders. We propose that cerebellar functioning is another risk factor that needs to be added to the diathesis of anxiety vulnerability. Continued research of individual differences in both cerebellar-modulated tasks (e.g., eyeblink) and the cerebellar role in higher cognitive tasks (e.g., stimulus processing, attention; emotional regulation) will shed light on the interplay of vulnerabilities contributing to the development of anxiety disorders.

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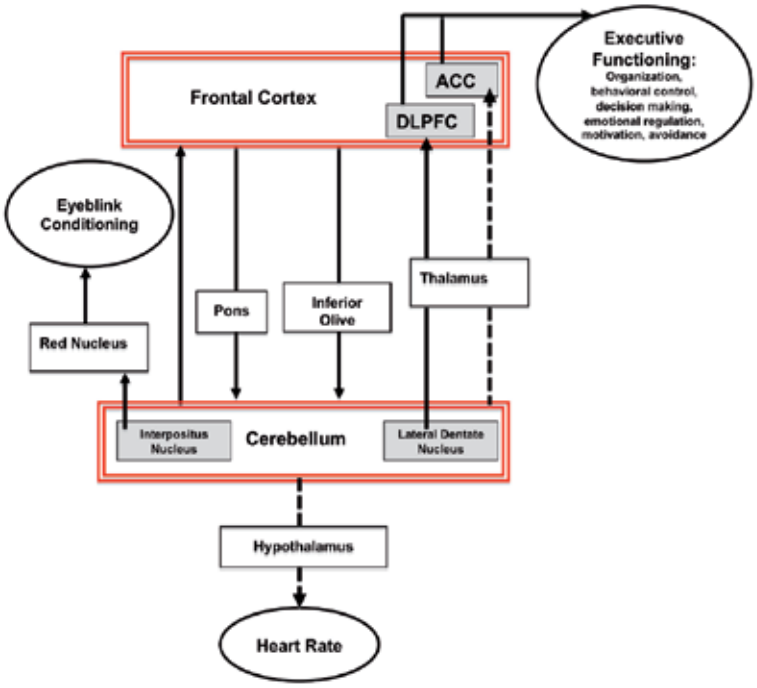

Figure 5. Cerebellar functional connectivity. Reciprocal connectivity with the cortex puts the cerebellum in a position to modulate higher cognitive processes via connections with the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). Many functions altered by at-risk temperament may be modulated by the cerebellum including eyeblink conditioning, heart rate reactivity, and executive functioning such as emotional regulation, motivation and avoidance.

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Chapter 4

Searching for Biological Markers of Personality: Are There Neuroendocrine Markers of Anxiety?

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Defining the concepts underlying differences in emotional reactivity

The existence of stable individual differences in cognitive and emotional capabilities both in animals and humans is well-accepted. The theories of personality assume that such individual differences can be categorized and that the richness of individual differences in humans would be the result of the combination of differences in a few underlying personality factors. The most accepted contemporary theory is that of "Big Five" [1] that consider five highest order factors: neuroticism, extraversion, openness, agreeableness and conscientiousness. However, the nature of some of the putative factors is still a matter of dispute in the different theories. Within this framework, the factors extraversion and neuroticism have been associated to the response to positive and negative emotions, respectively. Moreover, it is typically distinguished between personality and temperament, the latter term referring to biological predisposition that is noted early in life and will eventually lead to adult personality [2]. Emotionality may be considered as relatively stable individual characteristic so that subjects labeled as highly emotional will strongly react to emotional stimuli, particularly negative ones. It is of interest to know how high neuroticism subjects react to stressful situations and which are the consequences of such exposure. It has been reported that in response to an adverse event high neuroticism soldiers showed larger increases in psychiatric symptoms than low neuroticism subjects [3], but no differences in the response were observed after controlling for pre-trauma symptoms. These data question the existence of high stress responsiveness in high neuroticism subjects.

In animals, the concept of emotionality is associated with the response to aversive stimuli. On the basis of the study of the behavioral and physiological responses to emotional situa-

tions, it may be concluded that emotional reactivity is clearly multifactorial. For instance, neither behavioral nor physiological responses, all of them presumably related to this concept, follow a uniform pattern when different strains of rats are compared [4]. The obvious conclusion is that emotionality is a complex, multifactorial, concept [4] and that emotional stimuli are probably processed in parallel brain circuits thus resulting in a wide range of associated physiological responses.

For the purpose of the present review we will focus on individual differences in anxiety. This is a particular emotional characteristic that has attracted considerable attention for the important role of anxiety disorders in humans. It is generally distinguished between the concepts of trait and state anxiety. The first refers to a stable predisposition to react with low or high levels of anxiety in response to anxiety-provoking stimuli, whereas the second evaluate the actual reaction to a particular situation. Some classical psychometric test distinguish between both, for instance the trait-state anxiety Spielberger test or STAI [5], trait anxiety being a general predisposition to get higher levels of state anxiety when confronted with aversive situations. The distinction between trait and state anxiety is particularly difficult in animal models, although some authors assumed, in line with the concept in humans, that animals characterized by high levels of trait anxiety should show high levels of anxiety-like behaviour in response to different tests, as it is the case of BALB/c inbred mice [6]. There is no consensus about putative tests that can specifically evaluate differences in trait anxiety in animals. Another important theoretical consideration is the distinction between normal and pathological anxiety, the latter one reflecting merely the extreme of a continuum, or on the contrary qualitative differences with the normal population. This distinction is basically impossible to establish in animal models.

When discussing about animal models, it is important to distinguish between those that involve certain environmental or genetic manipulations aimed to develop high anxious individuals or those aiming at evaluating anxiety-like behaviour in particular individuals. We referred to the latter as tests for anxiety or anxiety-like behaviour. There are different animal tests for anxiety. Some of them involve unconditioned response to aversive stimuli, whereas others imply conditioned responses [6]. Even when unconditioned tests, which usually involve evaluation of the free behaviour of animals, are used there are many instances of dissociation in the outcomes of the different tests when comparing groups of animals [i.e. 7]. This suggests that each test probably evaluate situational-specific components of anxiety. In fact, factorial analysis sometimes supports that putatively underlying factors determining behaviour are likely to differ in great part across tests [i.e. 8,9]. This is important when considering the putative relationship between anxiety and physiological parameters to be discussed later. Nevertheless, marked differences in trait-anxiety, either of environmental or genetic origin, may result in important differences in several different behavioral tests [i.e. 10,11], suggesting partially common underlying factors.

It is now widely-accepted that there are conceptual differences between fear and anxiety in that fear is elicited by precise and temporally defined dangers (the presence of a predator, exposure to well-announced aversive stimuli such as electric shocks), whereas anxiety would be elicited by more diffuse and sustained dangers (contextual fear conditioning,

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predator odours, unpredictable aversive stimuli) [12, 13]. Nevertheless, it is still difficult to be sure whether behaviour of animals in novel environments is related to fear or anxiety. For instance, rats and mice have innate aversion for open spaces, likely to be related to the risks of being predated in such places. Can then we speak about fear (innate predisposition) or about anxiety so far as the open spaces is only potentially nor actually dangerous? This is important as several widely used anxiety tests are based on exposure to novel environments such as the elevated plus-maze (EPM) or the light-dark (or dark-light) tests [14-17]. The EPM consists of a plus-maze elevated over the floor, with two (closed) arms surrounded by walls and other two unprotected. The light-dark apparatus has two compartments, one small and dark and another much greater and illuminated. In the light-dark version we initially put the animals into the illuminated area and measure time spent to entry for the first time in the dark compartment, the number of transitions between light and dark and the time spent in each compartment. In the dark-light version, the animals are introduced into the dark compartment and we measure the latency to enter into the illuminated area and the other measures previously indicated. The EPM and light-dark test are based on the fear elicited in rodents (which are nocturnal animals) by open and illuminated spaces, and the natural tendency of these animals to explore new environments. These two tendencies generated a conflict and we expect that less emotional, fearless or low anxiety animals spend more time in the open arms of the EPM and the illuminated area of the light-dark test. Other animal models are based on the performance in an active avoidance-escape task in a shuttle box. In this task the imminence of a shock is signalled by a specific conditioned stimulus (noise, light; CS) and the animals can learn to avoid the shock (during the CS) or escape from the actual shock by doing a particular active behaviour: jumping from one side to the other. This procedure likely elicits an emotional reaction close to fear. However poor performance in such task is considered to be associated to high anxiety that makes the animals to become immobile and perform poorly. Administration of classical anxiolytic drugs clearly improves performance [i.e. 18]. The extent to which psychological dimensions underlying individual differences are similar in all cases or whether or not we are really detecting differences in anxiety is still an open question.

In addition to the problem of correctly indentifying a particular behavioral trait, there are problems related to the characterization of the physiological profiles associated to such a trait. First, negative emotional situations elicit a wide range of physiological responses and it is important to know whether or not such repertoire of responses is dependent of the particular stimulus or the particular emotion elicited. Until now it has not been possible to conclusively identify physiological response patterns associated to specific emotions. Second, the emotional response to particular situations are greatly influenced by the cognitive processing of the particular stimulus (appraisal) and by coping strategies, that is the behavioral repertoire used for the animals to escape from the source of the aversive experience or to reduce the impact of the situation. Koolhaas [19] considered coping style as a set of coherent behavioral and physiological responses to aversive stimuli. Two different coping styles have been defined: proactive (active) and reactive (passive), characterized by the triggering of active versus passive strategies to cope with aversive situations. The authors considered coping style as independent of emotionality [19,20]. That is, the dimension of active *versus* passive

strategies is considered as orthogonal to emotionality. Nevertheless, coping style can influence the success of the strategy used to face the situation and, indirectly, the behavioral and physiological response to the situation. Therefore, it is difficult to establish putative relationship between physiological variables and emotionality, including anxiety, without knowing other dimensions of personality as coping style.

It should be also taken into account that even if we can isolate one particular trait such as anxiety, the final behavioral and physiological responses (measurable outputs) are the result of the activation (or inhibition) of a wide range of divergent brain pathways, each of them putatively influenced by individual characteristics not related to the trait of interest, which may perturb or mask the common influence (trait) on all these variables. For instance, if we evaluate emotional reactivity by the activity of animals in a novel environment, even if two animals experienced the same level of fear/anxiety, the expression of the final measured response (ambulation, rearing) could differ because of different in activity, coping strategies (active or passive) or other traits (i.e. interest for novelty). Available evidence indicates that the genetic control of anxiety appears to be polygenic (as it is the case of other behavioral traits). Similar conclusion applies to the control of certain physiological parameters important for the present issue, as it is the case of the hypothalamic-pituitary-adrenal (HPA) axis [21]. By definition, inbred rats are genetically homogeneous and homozygotic for all genes. This means that every inbred strain has only a particular allele for each gene among the various ones present in the species and that throughout the process of inbreeding, a particular allele of each gene involved in the behavioral trait of interest or in the activity of the HPA axis has been randomly fixed. As it can be assumed that the genes are controlling each particular function in both positive and negative directions, each particular inbred strain could have been fixed a different combination of the alleles involved in the functions of interest. Therefore, it may be theoretically difficult to find a relationship between a behavioral trait and the HPA axis that may apply to other inbred strains or to an outbred population of rats. That is why we will refer only in very specific cases to studies with inbred rats or mice.

1.2. An overview of the HPA axis and other physiological stress markers

The present review will focus on the relationship between anxiety and the sympathetic-medullo-adrenal (SMA) and hypothalamic-pituitary endocrine axes. In the latter case, special attention should be given to the HPA axis and prolactin because they are considered as good biological markers of stress (see below). Activation of the SMA and HPA axes constitute the prototypical physiological responses to stressors in all vertebrates. These two axes have focused great attention in the field of stress for two main reasons [22]. First, the release of SMA and HPA hormones into blood is positively related to the intensity of the stressful situations and therefore they are well-suited to reflect differences among subjects in the degree of emotional activation. Second, activation of the SMA axis have a critical role in the regulation of metabolism and cardiovascular responses and is likely to be important for the development of certain stress-related pathologies (i.e. hypertension). Third, glucocorticoids (cortisol in humans and most mammals; corticosterone in rats and mice), the final output hormone of the HPA axis, has been implicated in a wide range of pathophysiological and

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psychopathological processes, including cardiovascular diseases, immune suppression, altered gastrointestinal function, anxiety disorders, depression and predisposition to drug self-administration. However, It is now well-recognized that stress-induced pathology is not only dependent on the nature and time-schedule of exposure to stressors but on individual differences in vulnerability to them.

The association between the activation of the SMA axis and stress is well-known since the earlier works by Cannon in the first half of the XX century. However, it is now realized that stress exposure also resulted in the activation of certain responses mediated by the parasympathetic nervous system. For instance, changes in intestinal colonic motility and visceral pain sensitivity [i.e. 23-25]. Moreover, the old idea that the SMA axis is activated in an all or none manner is not accepted as there are strong anatomical and functional evidence for a fine tuning of the response of SMA to different stimuli, including stressors [26, 27]. The flexibility of the SMA axis to respond to different stimuli is on the basis of the theories that argue that different emotions in humans can be distinguished by a particular physiological signature, nevertheless, there is not at present unequivocal and precise evidence for such signature [28]. Activation of the SMA axis have been typically evaluated measuring plasma (or urinary) levels of noradrenaline and adrenaline, heart rate (HR), heart rate variability (HRV, a measure of parasympathetic cardiac activity), diastolic and systolic blood pressure (DBP; SBP) and electric skin conductance. Plasma levels of adrenaline derived almost totally from the adrenal medulla, whereas plasma noradrenaline derived in part from the adrenal medulla but mostly from the activity of sympathetic nerves in all body. It is well-established that both plasma adrenaline and noradrenaline increases in response to emotional stressors, but the former better reflects the intensity of emotional stressors [29]. As circulating adrenaline is the main factor controlling stress-induced hyperglycaemia, it is not surprising that plasma glucose is a marker of stress intensity under moderate to strong stressful conditions [29].

The HPA axis is a complex and dynamic system whose regulation has been very well-characterized in the last decades [30]. The main brain locus of control of the HPA axis is the paraventricular nucleus of the hypothalamus (PVN). The PVN is a complex nucleus with two main types of neurons and several subdivisions. Big (magnocellular) neurons are located in the PVNm and synthesize the neurohypophyseal hormones oxytocin and vasopressin (VP), sending axons directly to the neurohypophysis. Small (parvocellular) neurons are concentrated in the PVNp and send axons to the median eminence to release ACTH secretagogues into the pituitary portal blood. Among such secretagogues, the corticotropin releasing factor (hormone) (CRF or CRH) is considered to be the most important in that it controls both synthesis and release of the adrenocorticotropic hormone (ACTH) and other peptides derived from pro-opiomelanocortin (POMC) in anterior pituitary corticotrope cells. Among the other ACTH secretagogues, VP appears to play a prominent role, acting synergistically with CRH to increase the release (but not the synthesis) of ACTH. In the PVNp appears to be two different populations of CRH neurons, one co-expressing and another one non-coexpressing VP. Interestingly, persistent or repeated activation of the HPA axis is accompanied by an increase in the number of CRH neurons coexpressing VP in the PVNp, suggesting a more

prominent role of VP in those situations associated to hyperactivity of the HPA axis. CRH in the anterior pituitary acts through CRH type 1 receptors (CRH-R1), whereas VP acts through AVP1b receptors. In addition to the above considerations, it should be taken into account that the contribution of CRF, VP and other secretagogues to the release of HPA hormones appears to be dependent on the particular type of stressor.

When the animals are exposed to stressful situations ACTH is promptly released (a few minutes), reaching a maximum between 5-10 minutes after a brief exposure to stressors or between 15-30 minutes with more prolonged exposures. Plasma levels of ACTH may well reflect a wide range of stressor intensities provided that samples are taken at appropriate times after the initial exposure to the stressor [29]. If exposure to a stressor lasts only a few minutes, maximal ACTH levels are achieved in a period of 5-10 minutes, then declining. If exposure to the stressor continues and it is relatively severe, the ACTH response is maintained for about 1 h but not more, and, therefore, plasma levels of ACTH are no longer a reflection of stressor intensity. One critical point regarding stress-induced adrenocortical secretion is that the maximum is reached with relatively low levels of ACTH so that plasma levels of glucocorticoids are only a good reflection of ACTH release with low intensity stressors. In fact, differences in plasma levels of corticosterone immediately after exposure to relatively severe stressors (i.e. footshock, restraint, immobilization) reflect more the maximal capability of the adrenal to secrete glucocorticoids, which is related to the adrenal weight [i.e. 31], rather than the circulating levels of ACTH, thus leading to a frequent misinterpretation of the results.

On the basis of the above, two major points should be considered in evaluating the impact of a stressor on the HPA axis. Firstly, measurement of circulating levels of glucocorticoids at a time shorter than 15 minutes after initial exposure to stress is non-appropriate to reflect the actual impact of a stressor on adrenocortical secretion because maximum levels are achieved nearly and beyond this time point. Secondly, plasma levels of glucocorticoids are not a reflection of stressor intensity above a certain level of intensity, which usually lies within low to moderate range. In the rat, exposure to a relatively stressful novel environment is probably the situation above which glucocorticoids hardly can detect actual anterior pituitary activation. Although, plasma glucocorticoids levels just after stress did not reflect ACTH levels, the follow-up of their plasma levels for a period of time after the termination of stress can reflect the initial ACTH release and therefore should be used in those cases where there is no possibility to directly measure ACTH.

Glucocorticoids release by stress exerts a wide range of actions in the body, both peripherally and centrally. These effects are exerted through genomic and non-genomic processes [32, 33]. Genomic effects of glucocorticoids are exerted through two well-characterized receptors: mineralocorticoid (MR, type I) and glucocorticoid (GR, type II) receptors. The non-genomic receptors are still uncharacterized at the molecular level, but are likely to be located in plasmatic membrane. Regarding the regulation of the HPA axis, one major function of glucocorticoids is to exert a negative feedback to reduce initial activation of the HPA axis. This negative feedback [34] is exerted at different levels: at the anterior pituitary, at the PVN and at other key brain areas such as the hippocampal formation and the prefrontal cortex

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[30]. The negative glucocorticoid feedback controls both normal resting activity of the HPA axis and the response to stressors. Since a defective negative feedback can markedly alter HPA functioning, there are classical tests for the efficacy of such feedback that use exogenous administration of natural or synthetid glucorticoids. In humans, it is extensively used the administration of the synthetic glucocorticoid dexamethasone (DEX) in the so called suppression DEX test. However, the validity of this test has been questioned by the fact that DEX, which easily penetrated the brain, is excluded from the brain by the multi-drug resistant protein P-glycoprotein [35]. Therefore, depending on the dose DEX mainly acts at the pituitary and only to a limited extent within the brain.

The HPA axis shows both circadian and pulsatile rhythms [36]. In addition to its biological meaning, the existence of a pulsatile secretion of ACTH and corticosterone is an important concern when only one sample is taken as it could not be representative of the actual secretion. Regarding circadian rhythm, maximum activity is observed around the awakening time. Maximum levels of plasma glucocorticoids are associated in all animals and humans to the start of the active period, being observed just around lights off in rats and mice and just after sleep in humans. Although the circadian rhythm affects both ACTH and glucocorticoids, the amplitude is much greater for the latter than for ACTH due to an increase in adrenal sensitivity to circulating ACTH [37]. In humans, there is a sharp increase in the first 30 minutes after awakening (called the cortisol awakening response, CAR) followed by a progressive decline over the day [38, 39]. Both in animals and humans, proper evaluation of the HPA axis requires taking several samples over the day.

Measurement of plasma levels of ACTH and corticosterone under resting (basal) conditions and after exposure to stress is the simplest approach when studying the functionality of the HPA axis. It is important to note that altered responsiveness of HPA hormones to stress can be observed with normal resting levels, but increased responsiveness to stressors may eventually result in increased resting levels of plasma glucocorticoids. However, these measures are very often insufficient for a deeper understanding of HPA differences between individuals or between different physiological or pathological conditions. Other classical measures include the evaluation of: (a) adrenal responsiveness to ACTH by administering exogenous ACTH and measuring plasma levels of cortisol or corticosterone; (b) adrenocorticotrope cell responsiveness to CRH and VP by exogenous administration of these neurohormones and measurement of plasma levels of glucocorticoids and preferable of ACTH; (c) the integrity of negative glucocorticoid feedback mechanisms, usually by given DEX. More recently, the combined DEX-CRH test has gained considerable interest, although the biological processes underlying this test are not well-understood. In animals, we can obviously use a wide range of additional approaches, but the most used are the evaluation of the brain expression of those neuropeptides directly related to the regulation of the HPA axis. If some subjects respond more to stress, it is assumed that they will ideally show enhanced PVN expression of CRH and/or VP, enhanced AP expression of the POMC gene, increased adrenal weight and perhaps higher resting levels of plasma glucocorticoids and reduced efficacy of negative glucocorticoid feedback. This is a typical pattern after exposure of animals to chronic severe

stressors [40]; however, it is realistic to assume that this whole pattern would be rarely found in humans.

Individual differences in some of the components of this complex biological system may oppose to the expected results, complicating the interpretation of the results. For instance, a highly emotional rat or mouse strain may be characterized by a physiological defect in the HPA axis (i.e. defective CRH production, reduced adrenocortical responsiveness to ACTH) that would act in the opposite direction to emotionality thus cancelling the differences in particular hormonal output. This is the case of inbred Lewis rats. They are considered as highly emotional [4], but are also characterized by a defective HPA system thus resulting in reduced ACTH and corticosterone response to a wide range of stressors (i.e. 41, 42). Therefore, if we expect higher HPA activation in these emotional animals (a hypothesis that is not necessarily true), defective HPA function could mask the expected higher HPA response. This problem is particularly important when comparing inbred animals.

In addition to the HPA axis, all anterior pituitary hormones (growth hormone, GH, thyrotropin stimulating hormone, TSH, prolactin, luteinizing hormone, LH, and follicle-stimulating hormone, FSH) have been extensively studied regarding stress and psychopathology. However, in recent decades, the interest focused on the HPA axis and to lower extent in prolactin. Prolactin is a stress-responsive hormone that is regulated by two hypothalamic mechanisms [43]. One involves a potent and tonic inhibitory control by a population of dopaminergic neurons located in the arcuate nucleus that send axons to the pituitary portal blood (tuberoinfundibular system). The other involves one or several prolactin releasing factors (PRFs). There are several candidates as PRFs, including oxytocin and VP, but there is no still agreement about the actual PRF. It is likely that during stress, prolactin release is the consequence of the reduction of dopaminergic inhibitory signals and the increase in stimulatory inputs. Although the precise role of prolactin during stress is not known, there is evidence that peripheral prolactin has access to the brain through prolactin receptors and can exert anxiolytic and anti-stress effects [44].

1.3. Are the intensity and nature of the stressor important for characterizing individual differences?

Which are the objectives of characterizing individual differences in responsiveness to stressors? One important purpose is to associate altered physiological responsiveness to pathological conditions: i.e., increased cortisol response to stressors may underlie immune suppression. Another one is to establish whether or not certain individuals or psychopathologies are characterized by an altered sensitivity to stressors. In the latter case, we assume that the chosen physiological variable is able to distinguish between hypo- or hyper-responsive subjects. However, to accomplish this goal we need to demonstrate first that these variables are able to reflect the intensity of stressors and that the results are relatively unaffected by the type (quality) of stressor. In animals, on the basis of neuronal activation as revealed by c-fos and lesion experiments it appears that those stressors having a predominant emotional component (i.e. electric shock, restraint, immobilization, exposure to predator or predator odors) activate the HPA axis following telencephalic pathways, whereas stressors

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having a predominantly physical component (endotoxin, cytokines, hemorrhage) act primarly at the level of the brainstem, brainstem nuclei sending stimulatory signals to the PVNp [45, 46]. In fact, recent studies suggest that is likely that each particular stressor can have a particular brain activation signature, thus leading to differential adaptive behavioral and physiological responses and pathological consequences [47]. Nevertheless, it has been demonstrated in rats and mice that in response to predominantly emotional stressors, plasma levels of adrenaline, noradrenaline, ACTH, corticosterone (under certain conditions) and prolactin reflect, under appropriate conditions, the intensity of stressors [29]. In contrast, whereas circulating levels of some other anterior pituitary hormones (GH, TSH, LH) are altered by stress in animals and humans [i.e. 48-51], there is no evidence that they are sensitive to the intensity of stressors. In rats, we have found a very consistent correlation between the ACTH or corticosterone response to different novel environments [52, 53], whereas no correlation at all when comparing the response to a novel environment and to a much more severe stressor such as immobilization (unpublished). Whether or not the critical factor for the lost of correlation is the markedly different intensity of the two stressors or the qualitative differences among them is unclear.

In humans, despite the extensive human literature on stress, there have been few attempts to establish which physiological variables may be sensitive to the intensity of emotional stressors. Callister [54] used two tests (a modified Stroop colour word test and mental arithmetic task) each with different levels of difficulty over one unique session and observed progressive increases in the perceived stress in function of the difficulty; in contrast, HR was independent and DBP and SBP promptly achieved a plateau with relatively low levels of intensity. Therefore, there is negative evidence for a relationship between HR and level of stress and limited evidence regarding blood pressure. In our own work we compared in Medicine female students the anxiety, cortisol, prolactin and glucose responses to two exams (Psychology and Physiology) that were known to induce different levels of anxiety [55]. As expected, state anxiety increased in response to both exams as compared to a regular day, but anxiety was greater with Physiology. The response to plasma cortisol was low, but in the same direction, whereas prolactin not only increased with respect to the routine day, but the increase was greater with Physiology than Psychology exam. In another study, salivary cortisol appears to reflect the degree of stress when assessed in different situations during military survival training [56]. These data support the hypothesis that biological stress markers are likely to behave similarly in humans and rodents. Interestingly, despite the parallel behaviour of state anxiety, cortisol and prolactin, no significant correlation was observed between the variables in our work [55], suggesting parallel but in great part independent regulation. The Trier social stress test (TSST) is an extensively used psychosocial stress that includes public speech and evaluation [57]. Subjects classified as high or low responders in function of the ACTH and cortisol responses to the TSST did not differ in their HR, adrenaline or noradrenaline responses [58]. This suggests that classification of subjects was based more on a specific functional difference in the regulation of the HPA or on individual differences in stress responsiveness that only affected the HPA axis, not reflecting a general stress hyper-responsiveness.

In sum, the available results are not suggestive of a stressor-independent pattern of response of the HPA axis and other variables that could unequivocally characterize individuals. That is, individual differences in physiological responsiveness to stressors are not only depending on certain characteristics of the individuals, but also on the particular stressor used as a challenge. Interestingly, attention should be paid as to how subjects can experience different emotional reactions to the same stressful situations. Thus, it was observed in healthy subjects a differential emotional response (evaluated by facial expression) to a mental arithmetic task that translated to a differential cardiovascular and salivary cortisol response [59]. In contrast, self-reported emotional experience did not contribute to such differential physiological response.

2. Neuroendocrinology of anxiety in humans

2.1. General considerations

In evaluating the neuroendocrinology of anxiety we can take some critical points into consideration. First, is there any relationship between state anxiety and certain hormones in response to some acute aversive situations? Second, is there any relationship between trait anxiety in a non-pathological population and resting or stress levels of hormones? Third, are resting or stress levels of hormones altered in pathological anxiety?

It is well-known in humans that exposure to acute stress can induce physiological (including hormonal) changes and increased anxiety, with a pattern quite similar to that observed in animals. However, there are numerous inconsistencies in the literature regarding the response of cortisol or prolactin to stressors. This is likely to be due to our poor knowledge on the dose-response relationship between stressor intensity and the elicited physiological and anxious responses in humans. The characterization of the dose-response curves of stressor intensity and physiological variables is critical for three main reasons. First, we can identify which physiological variables are actually sensitive to the intensity of stressors, thus ruling out those which are not. Second, we need to know which range of intensity of stressors can be appropriately evaluated using a particular variable. For instance, we know that in rodents plasma corticosterone is useful for low to intermediate intensity stressors but not for the intermediate-severe intensities, whereas the opposite is true for plasma glucose. Third, if the physiological response is well-characterized, this can help to objectively place any experimental stressful situation within the stress scale. Finally, and importantly, if we are using experimental situations eliciting a modest (or a very high) physiological response, the characterization of individual differences should be theoretically more difficult. This is particularly critical when the experimental conditions only elicited an extremely low, if any, response as appear to be the case in an important number of papers [for review, see 60].

In analyzing the literature about individual differences in responsiveness to stressful laboratory tasks, it is important to consider the importance of pre-task hormone levels. It has been repeatedly observed that some physiological markers of stress are elevated by the anticipation of the task rather than by the task itself. This sometimes leads to misin-

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terpretation of the results as a reduced response to the task. In fact, anticipatory anxiety and physiological response may be indicative of high rather than reduced responsiveness to putative stressful situations.

2.2. Neuroendocrinology of anxiety in healthy subjects

Unless otherwise stated, differences in trait or state anxiety were evaluated with the well-characterized STAI. We will comment first data regarding state anxiety and then trait anxiety.

Although numerous studies have demonstrated increases in both state anxiety and some physiological parameters in response to stressful situations, only few studies reported correlation between them. In an important number of studies correlation between state anxiety and some hormones was low or absent, suggesting that despite the apparent parallelism, underlying factors are likely to differ. In response to anticipation of surgery a significant correlation was observed between state anxiety and cortisol, but not prolactin [61]. In contrast, no association between anxiety and the increases in cortisol, prolactin or TSH levels were observed after parachute jumping [50]. In our own work with exam stress, no significant correlation was found between state STAI anxiety and plasma cortisol or prolactin levels [55]. Similarly, in a speech task, some correlations were found between certain physiological parameters (HR, BP, noradrenaline, cortisol), but not between them and state anxiety [62]. Pottier et al [63] observed in medical students that consultation in an unfamiliar ambulatory setting caused more anxiety (as evaluated by the STAI and a visual analog scale, VAS) and salivary cortisol response than consultation in a familiar (in-hospital) setting, but no correlation was found between the two measures. Similarly, VAS anxiety did not appear to predict changes in cortisol or HR response to the TSST test in young males whereas perceived stress did [64]. A study with arithmetic stress observed significant correlation between state anxiety and salivary α-amylase, but not cortisol or chromogranin-A [65]. Salivary α-amylase and chromogranin-A both reflect SMA activation, but it is possible that salivary α-amylase represents a specific component of SMA activation more closely related to anxiety than other SMA markers and cortisol. In contrast to most of the previous results, a study evaluating in surgeons the physiological and STAI response to 54 different surgical procedures (some of them not perceived as stressful) observed significant correlations between STAI and HR or salivary cortisol, and between HR and cortisol [66].

In conclusion, the above results did not reveal a consistent positive relationship between state anxiety and physiological response to stressors. One theoretical explanation for the inconsistencies may be explained by the type of data incorporated to the measurement of correlation. If we include data corresponding to different stressful situations differing in intensity and, therefore, in the magnitude of the response of certain variables (i.e. anxiety and cortisol), obviously both variables would increase in parallel. Consequently, a positive correlation should be observed (Fig. 1). In contrast, if we consider only the same data corresponding to each particular stressful situation, no correlation could be observed. In addition, there are other possibilities to explain this lack of consistent relationship. Firstly, failure to find association may be due to methodological problems such as the clearly different dy-

namics of each variable that make it very difficult to design experiments optimizing all variables. Secondly, physiological variables may capture specific psychological processes, only some of them being more specifically related to measures of anxiety. Finally, dissociation may exist between subjective and physiological measures of emotion. For instance, invasive cardiologists showed increased anxiety response when they adopted a secondary assistant (teaching) than a primary operator (autonomous) role, but this subjective state was not associated to higher HR and salivary cortisol responses [67].

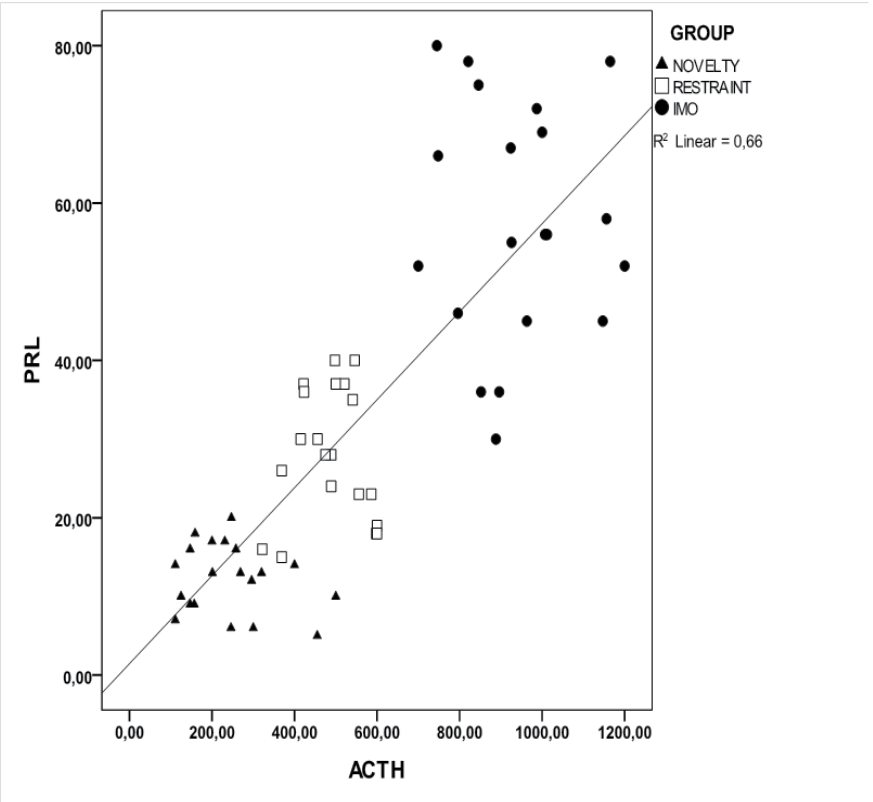

Figure 1. Correlation between two physiological measures (ACTH and prolactin, PRL) in a simulated response to three stressors of different intensity: a novel environment, restraint in tubes, and immobilization on boards (IMO). It should be noticed than when all samples are considered there is a positive statistical significant correlation between the two hormones, whereas no correlation at all was found when only samples corresponding to the same stressor were studied. This can explain inconsistencies in the literature regarding correlations between physiological variables and between them and state anxiety.

Regarding trait anxiety, there is negative evidence for an association between trait anxiety and salivary cortisol response to a speech task or the TSST in adult males [68. 69]. In a study that compared the response to the TSST of controls and patients with chronic atopic disease, the lack of relationship between trait-anxiety and salivary cortisol was confirmed and extended to plasma levels of ACTH [70]. Similarly, no relationship was found between trait

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and state anxiety and salivary amylase and cortisol responses to TSST or electrical stimulation either in males or females [71]. Surprisingly, some authors have reported a negative rather than positive relationship between trait anxiety and stress responsiveness. Healthy subjects classified as highly anxious showed a diminished salivary cortisol response to an unpleasant film as compared to low anxiety subjects [72]. This result has been extended in two studies showing lower plasma ACTH, cortisol, prolactin, adrenaline and noradrenaline in response to psychosocial stress (public speech) in anxious versus non-anxious subjects [73, 74]. Moreover, similar results were obtained using the Hospital Anxiety and Depression Scale that evaluated BP, HR and salivary cortisol responses to a combined (Stroop test, mirror-tracing and speech) psychosocial stressor [75]. The above data thus suggest a negative rather than positive relationship between neuroendocrine markers and trait anxiety, although neurobiological underpinnings are unknown.

The relationship between trait anxiety and resting activity of the HPA axis has also attracted attention. There is no association with basal salivary evening cortisol [76] or the cortisol response to the DEX+CRH test [77]. However, trait anxiety appears to affect the circadian rhythm of salivary cortisol in military men under free-living conditions, those with high trait anxiety displaying less pronounced decreased from early morning to mid-morning [78]. In post-pubertal adolescents, high trait anxiety resulted in higher evening salivary cortisol with no differences in morning levels [79]. Taken together, trait anxiety may be associated to a dysregulation of circadian resting cortisol levels, particularly the decline over the waking period, although there are discrepancies in the details. Studies measuring ACTH are needed to discern between ACTH-dependent or ACTH-independent dysregulation.

Interestingly, in response to a stressful video (corneal transplant) where higher and faster increased was observed in saliva α-amylase than in cortisol, a significant positive correlation was observed between trait anxiety and α-amylase, but not cortisol [80]. A recent report in children exposed to 3 consecutive stressors (including performance and peer rejection) confirmed the positive relationship of trait anxiety (measured by the revised children's manifest anxiety scale) and baseline or stress levels of α-amylase [81]. Considering the previously discussed positive relationship between α-amylase and state anxiety, this parameter offers promising results in studies of anxiety.

2.3. Neuroendocrinology of anxiety disorders

The relationship between anxiety disorders and basal (non-stress) levels of classical stress hormones is not clear. There are different types of anxiety disorders, as defined by the DSM-IVR [82]: Panic attacks, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder and generalized anxiety disorder (GAD). We will focus mainly in GAD on this aspect as an example among the different anxiety disorders.

Measures of urinary cortisol give inconsistent results, whereas higher catecholamine content appears to be more consistent in patients (see review of earlier works in [83]). Plasma prolactin was found to be normal in early studies [83] and this was further confirmed [84]. Cerebrospinal fluid (CSF) levels of CRH are considered as an index of overall activity of brain CRH neurons, including those neuronal CRH populations not directly related to the regula-

tion of the HPA axis. It appears that CSF CRH levels are not altered in GAD, suggesting normal brain CRH function [85]. In addition to the inconsistencies of early studies, data from some recent studies using salivary cortisol do not offer a clearer picture. In late-life GAD, increased resting levels of salivary cortisol were observed at several times in the morning but not the evening and the levels were positively related to the severity of anxiety [86]. In accordance, slightly higher awakening levels of cortisol were observed in a sample of patients with anxiety disorders, the effects being particularly significant in those with panic disorder with agoraphobia and those showing comorbidity with anxiety and depression [87]. In contrast, lower CAR was observed in another study with a large cohort of older adults with several types of anxiety disorders when compared to healthy controls [88]. No differences were observed at other times. Another study with middle-age people suffering from GAD showed no differences from controls either in the CAR or in the daily pattern of cortisol, despite higher levels of α-amylase [89]. Whether or not the inconsistencies are due to the age of patients or confounding factors is not known, although the latter concern should be taken into account considering the usually small magnitude of the effects. Quite interestingly, decreased levels of hair cortisol were recently observed in GAD patients despite no changes in salivary cortisol over the day under resting conditions [90]. As hair cortisol represents the integration of cortisol release over periods of months, the results support a negative relationship between GAD and HPA activity. It is unclear whether these patients show reduced response to daily stressors (and therefore, less release of cortisol) rather than reduced resting activity. This hypoactivity of the HPA axis does not appear to be a general characteristic of all anxiety disorders. Thus, slightly alterations in circadian and pulsatile secretion of cortisol and to a lesser extent in ACTH was reported in panic patients, with overall higher levels as compared to controls and increased amplitude of cortisol pulses [91].

Unfortunately, there are scarce studies on the comparison of the response to stress of GAD patients as compared to controls. In adolescents with GAD, increases in ACTH, GH and prolactin (but not noradrenaline, adrenaline and cortisol) were found in the phase of anticipation to the task in GAD patients but not in controls [92]. In contrast, no response to the task was observed.

Phobic subjects offer an interesting model for the study of the relationship between behavioral reaction to the situation and the concomitant physiological response. Severe anxiety was reported in patients with phobia to insects and small animals after forced exposure, whereas no changes were found in prolactin [93]. In a further study, increases in HR, blood pressure and plasma levels of adrenaline, noradrenaline, cortisol and GH were reported, although the increases in state anxiety were stronger and did not correlate to physiological responses [94]. The strong dissociation between subjective behavioral arousal and cortisol response to spider phobia was confirmed in another study comparing phobics and healthy controls [95]. Driving phobics as compared to controls showed increased anticipatory anxiety and cortisol response to driving, with further increases in anxiety but not cortisol during driving [96]. Moreover, no significant correlation was found between anxiety and cortisol in phobic subjects. Less clear is the response of social phobia patients to social stimuli. Salivary cortisol response to the TSST was similar in social phobic adolescent girls than in controls [97]. In

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contrast, in another study, children with social phobia showed greater trait anxiety (measured by the STAI for childrens, STAI-C) and also greater state anxiety and cortisol responses to a public speaking task than controls [98]. In the latter study, trait anxiety was positively related to cortisol, but it was not described whether both control and patients, which already differed in trait anxiety, were included in the same analysis. In children with social phobia, exposure to an adapted TSST resulted in higher baseline and TSTT-induced anxiety (scales for Iconic self-assessment of anxiety in children) than controls [99]. In physiological terms, baseline HR was higher and the response to the stressor lower in patients as compared to controls, whereas salivary cortisol and α-amylase response tended to be lower. Finally, a study comparing healthy controls, social phobia and post-traumatic stress (PTSD) patients showed higher salivary cortisol response to the TSST in social phobics as compared to controls and PTSD [100]. The authors also reported a positive correlation between cortisol response to the TSST and avoidance of angry faces in social phobics but not in controls. Taken together, all those data suggest at least a lower physiological than subjective response to the phobic situations.

Perhaps the strongest evidence for dissociation between subjective and physiological responses comes from patients with panic disorder. These patients have been studied during spontaneous panic attacks, after pharmacological provocation of panic attacks or in response to different types of stressors. During spontaneous attacks, despite strong subjective anxiety and physiological signs, changes in HR were not strong and changes in hormones (noradrenaline, adrenaline, GH and cortisol) were low and inconsistent, being the increases in prolactin the most consistent [83, 101]. When agoraphobic subjects were exposed to the phobic situation to trigger a panic attack, most of them experienced panic attacks while control subjects did not [102], but only the HR was higher in patients than in controls, whereas other measures (i.e. blood pressure, cortisol, prolactin or GH) did not differ. There are several pharmacological manipulations (i.e., lactate, CO2 inhalation, cholecistokinin-4, pentagastrin, doxapram or meta-chlorophenylpiperazine, m-CPP) that have been demonstrated to induce panic attacks only in a few healthy subjects, whereas they strongly induce panic attacks in almost all panic patients. This experimentally controlled approach has been extensively used to compare the physiological response (including GH, prolactin and cortisol) of panic patients and control subjects, but the results are difficult to interpret because of the effects of these manipulations on physiological variables. For instance, m-CPP is a serotoninergic drug that can pharmacologically induce the release of cortisol and GH. If the greater panicogenic effect of the drug on panic patients is paralleled by a greater cortisol and GH release [103], this can be interpreted as a parallelism between the subjective state and hormones, but also as a putative sensitization of brain serotoninergic pathways controlling these hormones in panic patients. Nevertheless, the overall conclusion is again that there are no parallelism between the strong anxiety- and panic-inducing effects of these manipulations in panic patients as compared to controls and the physiological response [104-111].

Finally, some studies aimed at characterizing the physiological response to stressors in panic patients. Fully remitted, medication-free panic patients exposed to a mild psychological stressor showed a clear anticipatory DBP response and a greater cortisol response

to the stressor as compared to a normal population [112]. In another study, in response to public speaking, anticipatory anxiety developed in medication-free symptomatic patients as compared to normal subjects, whereas the anxiety response to the actual stressor was lower [113]. Salivary cortisol showed an anticipatory response, with no further response to the stressor [114], whereas a permanently higher (anticipatory) skin conductance was observed in patients that did not further respond at all to the stressor [113]. No differences were observed in HR, DBP and SBP. The anticipatory plasma or salivary cortisol responses were not detected in a study using the TSST as the stressor that nevertheless showed markedly reduced plasma and saliva cortisol responses in panic patients as compared to controls, associated to a normal HR response [115]. In a very recent report using mild shocks as the stressor, the anxiety and salivary cortisol and α-amylase response was studied in panic patients as compared to controls [116]. Then, patients were treated with the benzodiazepine anxiolytic alprazolam and classified as responder and non-responder to the therapy. When the two groups of patients and controls were retrospectively compared, it was found a similar anticipatory increase in anxiety in the two groups of patients as compared to controls, but an anticipatory increase in α-amylase (but not in cortisol), only in those panic patients who further responded to the therapy with alprazolam. The similar state anxiety response of responders and non-responders accompanied by a differential anticipatory cortisol and α-amylase response demonstrates again the dissociation between subjective and physiological measures.

Table 1 summarizes the relationship between anxiety and the neuroendocrine response to stressors in healthy people and with anxiety disorders. The experimental data indicate a lack of parallelism between subjective state or trait anxiety and neuroendocrine response to stressors in healthy subjects. In fact, there is some evidence for a negative relationship between trait anxiety and physiological response to stressors. Regarding anxiety disorders, a negative relationship is frequently observed in panic and GAD patients, and a lack of association in social phobia.

3. Emotionality, anxiety and neuroendocrine markers in selected rat lines

3.1. Selection on the basis of defecation rate: Maudsley reactive (MR) and Maudsley non-reactive (MRN) rats

The first genetic selection of a putative emotional strain of rats used the criterium of defecation rate in a novel, stressful, environment (an open-field) and led to the characterization of high defecation rate (MR) and low defecation (MRN) lines [see 117]. This selection also resulted in lower activity in the open-field of MR as compared to MNR rats, thus supporting the hypothesis that emotional animals would display a lower level of activity in a stressful, environment. However, it soon became evident that the relationship between defecation rate and activity in the open-field was more controversial than previously assumed and of much lower magnitude than that of defecation. In addition, not consistent differences have been observed in other anxiety test, including the EPM, the acoustic startle response (ASR), the

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light-dark test and the shock-induced conditioned suppression of appetitive operant task [118-121] perhaps related to the existence of two different stocks of rats (UK and USA). Unfortunately, there only two reports comparing the HPA response in the two strains: Abel et al [122] found no differences in plasma corticosterone levels after 10 minutes of exposure to an open-field or to forced swimming. However, Kosti et al. [123] observed greater ACTH response to restraint in MR vs MNR, despite no differences in plasma corticosterone. This apparent discrepancy is likely to be due to increased corticosterone responsiveness to ACTH in MNR. Therefore, MR and MNR, which differ in some aspects of emotionality but not clearly in anxiety-like behaviour, did appear to show differences in HPA function.

Population	**Physiological system**					
	SMA		**HPA**		**PRL**	
Healthy subjects						
State anxiety	≈ *		≈		≈	
Trait anxiety	≈ / ↓		≈ / ↓		≈ / ↓	
Anxiety disorders						
GAD	↓		A / ↓		A / ↓	
Phobia	phobic Ss	others	phobic Ss	others	phobic Ss	others
	↓	?	↓	?	↓	?
Social phobia	≈	?	≈	?	?	?
Panic	panic attack	others	panic attack	others	panic attack	others
	↓	A / ↓	↓	A / ↓	↓	?

≈ : no correlation or approximately normal response (* except α - amylase, see main text)

↓: reduced, at least with respect to subjective anxiety

A : anticipatory response

Ss: stimuli

? : not tested

PRL : prolactin

Table 1. Relationship between normal or pathological anxiety and physiological response to stress.

3.2. Selection on the basis of the EPM: high anxiety and low anxiety rats (HAB, LAB)

The only specific selection process aiming at selecting two strains of rats strongly differing in their performance in the EPM, the most widely used test for anxiety, has resulted in HAB and LAB rats, the former displaying very low levels of exploration of the open arms of the plus-maze [124]. In addition, HAB rats spent less time in light and make less number of transitions in a dark-light test, and also spent less time in the social interaction test [125], confirming differences in anxiety. It is important to note that HAB rats are less active in the forced swimming test [124, 126], a classical test to evaluate antidepressants [127], which pre-

sumably evaluates passive-active coping strategies [128]. Therefore, HAB rat appear to be prone to use passive coping strategies and to depression-like behavior.

HAB showed greater ACTH and corticosterone responses than LAB, mainly when the animals are forced to remain in the open arms (more stressful than the closed arms) of the EPM [129], but not when they can freely explore both open and closed arms [124]. Moreover, no differences were observed in the ACTH and corticosterone responses to forced swim, despite differences in behaviour [124]. Surprisingly, HAB rats showed lower ACTH response than LAB to social defeat [130], demonstrating that differences in responsiveness to stress was dependent on the particular type of stressor used. Therefore, extreme differences in anxiety, evaluated by the EPM, only resulted in consistent differences in the HPA response to situations similar to those that serves as criteria for selection. When exposed to other situations, the results can markedly change. These data are very important because they suggest that individual differences in HPA responsiveness to stress are critically dependent on the type of stressor used.

HAB-LAB rats likely represent the most complete characterization of genetic differences in the HPA axis. In several reports it has been demonstrated enhanced VP gene expression in the PVN, affecting both magnocellular and parvocellular subdivisions [131]. In another report, enhanced PVN CRH expression was also observed [132]. These data suggest increased drive to the corticotrope cells, what is supported by an enhanced POMC gene expression in the anterior pituitary [133]. No differences were observed in CRH-R1 in the anterior pituitary, whereas there were increases in CRH-R2 (the other type of CRH receptor) and V1b receptors in the HAB rats [134]. It is quite possible that VP is responsible for the enhanced ACTH response to the DEX+CRH test in HAB rats [131], as the ACTH response to the mere administration of exogenous CRH was normal [135] and there are no differences between lines in the expression of GR in the anterior pituitary [131, 133]. Although most of the above described changes in the central aspects of the HPA axis may be better ascribed to depression-like rather than anxiety-like behavior, administration of an VP receptor antagonist in the PVN normalize anxiety-like behaviour of HAB rats [134]. This strongly suggests that enhanced PVN VP expression plays a critical role in anxiety.

The data regarding the PVN and the anterior pituitary would suggest increased drive to the gland and a generalized greater ACTH response to stress in HAB rats. However, this is not the case as reported above. A greater adrenal gland is associated in a normal population of rats with greater maximal corticosterone secretion [31]. Therefore, the increased adrenal cortex size of HAB rats is compatible with a greater maximal corticosterone secretion. In fact, HAB rats showed a normal ACTH response to endotoxin accompanied by a greater corticosterone response [136], which is likely to be maximal secretion under these conditions.

3.3. Selection on the basis of active avoidance performance

Several pairs of rat lines have been obtained on the basis of performance in passive or active avoidance tasks in a shuttle-box, using electric footshock as the aversive stimulus. Some, but not all, of these strains appears to differ in emotionality, particularly in fear/anxiety, but is should be taken into account that even if they actually differed in anxiety, also could differ in other

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traits (i.e. novelty-seeking or depression like behavior) that may affect the neuroendocrine response. These caveats should be taken into consideration in the discussion that follows.

The outbred Roman high avoidance (RHA) and Roman low avoidance (RLA) rats were obtained by genetic selection on the basis of performance in a two-way active avoidance task [see 20]. Most of the behavioral and endocrinological studies have been obtained in different substocks of the swiss sublines (RHA/Verh, RLA/Verh) and later by inbred RHA and RLA strains. It was soon realized that the two lines differed not only in active avoidance, but also in terms of emotionality, the RLA rats being more emotional than RHA rats. Subsequent research has demonstrated that the two lines differ in several important behavioral traits, including coping style and impulsivity [20]. The lines differ in some tests of anxiety more markedly than in others, being particularly relevant the inconsistencies regarding the EPM [137].

There have been some discrepancies regarding the responsiveness of the HPA axis to stress in these strains. In 1982, Gentsch et al. [138] firstly reported that RHA/Verh rats showed lower ACTH, corticosterone and prolactin responses to mild stressors (i.e. novel environments) than RLA/Verh rats, but the differences disappeared with stronger (i.e. ether stress, footshock, restraint) stressors. However, inconsistent differences were observed in when the lines were maintained in another laboratory [139, 140]. The study by Walker et al [141] is one of the most complete characterizations of differences in the HPA axis between the two lines. Unfortunately, the results are extremely difficult to interpret. Thus, it was found in RHA as compared to RLA rats: (a) higher adrenal weight; (b) higher basal levels of ACTH accompanied by normal corticosterone levels; (c) no differences in ACTH levels after 10 minutes of exposure to a novel environment or ether (10 minutes), despite an enhanced anterior pituitary response to exogenous CRH administration; (c) a lower corticosterone response to stressor despite the normal levels of ACTH and the increased adrenal weight. In addition, a higher number of GR in the pituitary along with higher MR levels in the hippocampus was found in RHA rats. The higher number of GR in the anterior pituitary may have contributed to the reduced ACTH response to CRH, whereas the higher MR in the hippocampus could be expected, if any, to reduce ACTH response to stress, which was not the case (in absolute terms) in their paper. In further reports, the early findings of increased ACTH and corticosterone responsiveness of RLA rats to novel environments were confirmed [137, 142]. Moreover, RLA rats showed normal levels of CRF mRNA, but increased levels of VP mRNA in the PVNp [142], a pattern observed in situations characterized by a chronic hyperactivity of the HPA axis. At first glance, the latter results suggest that HPA axis of RLA may be generally more responsive to stress than RHA, thus resulting in increased VP gene expression in the PVN. However, one could expect a greater relative adrenal weight in RLA as a consequence of the cumulative impact of higher ACTH response to daily events, but the opposite has been repeatedly found [139, 141, 143]. The possibility remains that the greater adrenal weight of RHA vs RLA rats is a compensatory mechanisms to maintain appropriate adrenocortical secretion despite some defect at the level of the adrenal.

Genetic analysis of cosegregation of different behavioral and physiological variables in these lines has allowed to conclude, in accordance with the inconsistency of the HPA data, that prolactin, but not the variables related to the HPA axis, is probably related to differences in active

avoidance [143]. Even if RLA are characterized by a greater HPA reactivity, the possible influence of behavioral traits other than anxiety on the HPA axis should not be disregarded.

After inbreeding (RHA-I, RLA-I), we have reported normal resting levels of ACTH and corticosterone, but increased response of the two hormones to a novel environment [144]. Enhanced PVN CRH gene expression, but unaltered VP expression in PVNp and PVNm, was also observed in RLA-I versus RHA-I. Quite interestingly, enhanced CRH expression in the RLA-I rats was found in a brain area, the dorsolateral division of the bed nucleus of stria terminalis (BST). As the BST has been repeatedly implicated in the control of anxiety [13], our data suggest that extra-PVN changes in CRH gene expression may participate in some of the behavioral differences between the two strains.

Syracuse Low and Syracuse High avoidance (SLA, SHA) rats, have been also selectively bred on the basis of their behaviour in an active avoidance task (see [145]). Again, SLA and SHA rats appear to differ in emotionality. Thus, SLA rats defecate more in an open-field and show faster learning of a passive avoidance task and more fear conditioned suppression of appetitive instrumental behaviour than SHA, but no differences were observed in sensitivity to shock or activity. Unfortunately, it is not known whether they differ in anxiety as evaluated by the EPM. In accordance with their greater emotionality, SLA rats show a greater glucose response to an open-field [146]. However, SLA rats are characterized by modestly lower corticosterone response to ether stress, but much lower adrenal corticosterone content, as compared with SHA [147]. Similar results were observed after exogenous CRH administration [148]. Quite surprisingly, reduced adrenal corticosterone levels occur despite greater relative adrenal weight and greater size of adrenal cortex in SLA rats [148, 149]. The most likely explanation is that RLA showed a defective adrenocortical responsiveness to ACTH that tended to be compensated by increased adrenal mass. Unfortunately, ACTH levels were not measured in any experiment.

In conclusion, the comparison of the neuroendocrine characteristics of RLA-RHA and SLA-SHA is limited by the lack of information regarding the last pair of lines. Nevertheless, the available information does not reveal a homogenous pattern. Accordingly, in mice, the best performed studied compared several inbred strains of mice in several test for anxiety (EPM, ASR and hyponeophagia) and in basal and stress levels of corticosterone [150]. Whereas a good correlation among the strains was observed with the three tests of anxiety, no correlation was found between anxiety-like behaviour and corticosterone. These data support conclusions in rats.

4. General conclusions

The overall conclusion of the present review is that the physiological response does not reflect concomitant changes in objective anxiety as evaluated by classical tests in laboratory animals or self-reported measures in humans. There are several reasons that can explain such dissociation and the sometimes controversial results. First, the uncertainty about the underlying psychological or behavioral traits of interest and the way we can evaluate them.

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Second, the use of animal lines differing in more than one trait, making difficult to separate the contribution of anxiety from that of other traits. Third, the different dynamics of the behavioral processes and the physiological variables measured. Four, the possibility that others, still not characterized, biological parameters may be more appropriate as biological correlates of anxiety. Finally, there are uncertainties about the relationship between subjective reports of anxiety and the biological response to aversive stimuli.

In laboratory animals, the classical approach has been the selection of the animals in function of particular criterium or test, assuming that this identifies the particular trait of interest, anxiety for the present discussion. However, it is unrealistic to assume that the selection of animals on the basis of one single test can really identify one particular trait. In addition, the experimental evidence strongly indicates that these animals also differ in other different traits, making it difficult to isolate anxiety for other traits. For instance, HAB-LAB rats not only differ in anxiety but also in depression-like behavior [124]. Similarly RLA and RHA rats also differ in impulsivity [137].

The most widely used physiological responses are those related to the SMA and the HPA axis, in addition to other hormones such as prolactin. The different indices greatly differ in terms of the time needed to reflect changes in the environment. Cardiovascular changes (i.e. HR, blood pressure) can rapidly change in one minute, plasma levels of adrenaline and noradrenaline is also very fast and their half-life is very short, thus resulting in the possibility of marked changes in periods of 5 minutes. Plasma levels of anterior pituitary hormones are released very fast (a few minutes), but half-life is longer than that of catecholamines (between 5 and 30 minutes or more, depending on the particular hormone). Finally, changes in plasma or salivary cortisol are relatively slow, with maximum no more than 15-30 minutes after the initial exposure to the situation. Thus, the dynamics of the response is important when considering the influence of cognitive processes in the regulation of the emotional response to the situation.

Although more elaborated endocrinological studies may help to elucidate some controversial results, it is important to look at other physiological variables. For instance, a recent study observed lower plasma levels of nesfatin-1, a recently characterized satiety molecule, in GAD patients [151]. Immunological markers are currently studied regarding stress and personality factors. In one interesting paper in a large population of men and women, anxiety positively correlated to levels of certain inflammatory markers (C-Reactive Protein, interleukin-6, Tumor Necrosis Factor-α and fibrinogen) [152]. Characterization of putative inflammatory markers of anxiety requires further studies.

In humans, psychological traits are complex constructs that involve top-down cognitive processes. In contrast, physiological response to aversive situations is likely to be reflexive in nature at least initially. It is possible that both processes are relatively independent. Rapid attention and responding to putatively threatening stimuli is a characteristic of several anxiety disorders and healthy people with high neuroticism or trait-anxiety [153]. In a very interesting study, preconscious and conscious attention biases to emotional stimuli were evaluated in subjects exposed 4 and 8 months later to a laboratory stressor or to examination, respectively [154]. Preconscious negative bias processing was a better predictor of cortisol response than self-reported neuroticism, trait-anxiety or extraversion.

Another additional problem when addressing human data is the limitation of the information we can obtain from typical laboratory stressors. First, emotional processing of stressors may be complex and dependent on the particular nature of the situation. Anxiety disorders may be associated to a differential processing of certain categories of stressors but not all stressors and therefore information obtain from exposure to standard stressors may be limited and different depending on the particular type of anxiety disorder. Second, laboratory stressors tend to be of lower intensity that some real-life stressors and it is unclear whether or not we can extrapolate the results from one type to the other.

Even if we can identify physiological variables related to pathological anxiety, an important concern is whether these variables are the consequence of the pathology or a predisposing factor. In the last year particular attention has been paid to this problem, but it is still an important drawback when analyzing published data.

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Chapter 5

Alterations in the Immune Response, Apoptosis and Synaptic Plasticity in Posttraumatic Stress Disorder: Molecular Indicators and Relation to Clinical Symptoms

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Additional information is available at the end of the chapter

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1. Introduction

Posttraumatic stress disorder (PTSD) (ICD-10 codes: F43.1, F62.0; DSM-IV-TR code: 309.81) [1, 2] is a complex severe and chronic psychiatric illness influenced by environmental and genetic factors [3-10]. PTSD is an anxiety disorder developed in a person experiencing, witnessing, or learning about an extreme physically or psychologically distressing event, associated with unprecedented violence [11, 12]. Traumatic events that can trigger PTSD include massacres, mass murder scenes, international, civil, political, ethnic and religious wars, genocides, natural and man-made disasters, criminal assaults, serious accidents, terrorist attacks, incarceration, trafficking, rape and other types of sexual assaults [12-17], life threatening illness and the sudden death of a loved one, serious medical illness, injury, surgery, hostage, kidnapping, difficult labors, etc [18-20]. Individuals who experience a trauma of this nature may develop symptoms that fall into three distinct clusters: re-experiencing phenomenon; avoidance and numbing; and autonomic hyperarousal. Symptoms usually begin within the first 3 months after the traumatic event and last for many years, although there may be a delay of months, or even years, before symptoms appear. PTSD patients are characterized by severe emotional state, sharp reduction in adaptive and information receiving abilities. They usually remain out of society, become drug addicted, alcoholic and often commit suicide [21-24]. Degrees of risk to develop PTSD from different traumatic events are presented in table 1.

It was shown that 37% of Cambodian refugees, 86% of women refugees in Kabul and Pakistan and 75% of Bosnian refugee women suffer from PTSD. In USA 60% of female rape sur-

vivors and 35% of UK adult rape victims are affected by PTSD. Similar to adults, some children, who witness or experience traumatic events, develop PTSD. Thus, in the USA 90-100% of children, who witness a parental homicide or sexual assault, develop PTSD, and in the UK 50% of sexually abused children are affected by this disorder [25-27].

Equally as staggering are statistics, which monitor the incidence of PTSD among combat veterans. Here, 30% of the American Vietnam veterans and 56% of Australia's Vietnam War veterans, 10% of Desert Storm veterans, 31% of Australia's Gulf War veterans, 6-11% of Afghanistan veterans and 12-20% of Iraq veterans in the US suffer from PTSD [25-28].

Statistical data also demonstrates that women are more than twice as likely to develop PTSD as men. Available data suggests that about 8% of men and 20% of women go on to develop PTSD [26, 29-31]. Is was also shown that PTSD is most often developed in representatives of national minorities, people surviving stressful events at list once in their life, as well as in people with low level of education, mental problems, having mentally ill family member or experiencing lack of support from their family members or friends [26, 29-31]. Currently, for about 7-8% of the USA population, 2-3% of the UK population, 6.4% of Australians and 3% of Cambodians suffer from PTSD [26-28].

Traumatic event	Degree of risk, %
Rape	49.0
Other types of sexual violence	23.7
Physical violence, severe beating	31.9
Accident and/or serious injuries	16.8-20.0
Stabbing, shooting	15.4
Sudden death of a family member or friend	14.3
Child's life-threatening illness	10.4
Murder, death or serious injury witness	7.3
Natural disasters	2.0-3.8
- hurricane	30.0-50.0
- tsunami	32.0-60.0 / 26.0-95.0
- earthquake (adults/youths)	
Man-made disasters	29.0
Terrorist attacks	28.0

Table 1. Risk for developing PTSD depending on traumatic event [25-27]

In Armenia PTSD is quite common as well, and is basically found among the descendants of Armenian Genocide victims, including current generation, combatants, refugees and victims of earthquake [32-40]. Thus, according to Goenjian et al, 73% among 1988 Spitak Earthquake

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survivors developed PTSD 4.5 years after the disaster [36]. In general, 10% of the world population is suffering from PTSD, and 70% is under the risk of developing PTSD [26-28].

Patients with PTSD have a reduced quality of life, an increased number of suicides and hospitalizations, high frequency of depressions, alcohol and drug abuse; social, family life and work become impossible.

Molecular mechanisms of generation and development of PTSD and their relation to the clinical psychopathologic criteria of this disorder are not clear yet. The lack of knowledge in this field significantly limits the development of effective therapeutic approaches for treatment of PTSD-affected subjects and prevention of further complications.

2. Neuroendocrine alterations in PTSD

PTSD is characterized by the central and autonomic nervous systems hyperarousal that is caused by functional changes in the limbic system, which is located between the brainstem and the cerebral cortex and coordinates their activities. This part of the brain regulates survival behaviors and emotional expression, being primarily concerned with tasks of survival such as eating, sexual reproduction and the instinctive defenses of fight and flight. It also plays a central role in memory processing. The hippocampus and amygdala, parts of the limbic system, regulate learning, memory, and emotion. The amygdala is important for the regulation of emotional memories, particularly for fear causing memories. It has been proven that amygdala is activated in the extreme situations. The hippocampus, on the contrary, is suppressed in these conditions. It has been shown that PTSD is characterized by functional hyperactivity of the amygdala and hypoactivity of the hippocampus [41-43].

A number of data suggests that alterations in the hypothalamic-pituitary-adrenal (HPA) axis and sympathoadrenal system (SAS) play a leading role in PTSD pathogenesis [13, 14, 44]. Thus, PTSD, as compared to norm, is characterized by low cortisol levels in plasma and saliva [45], whereas elevated levels of dehydroepiandrosterone (DHEA) and DHEA-sulfate are detected in this disorder [44-46]. Moreover, increased levels of corticotrophin realizing hormone positively correlated with the high levels of cortisol in cerebrospinal fluid of PTSD patients were observed [47]. Also, PTSD is characterized by increased glucocorticoid receptor sensitivity [48]. An increased levels of noradrenaline, neurotransmitter of central and peripheral sympathetic (adrenergic) nervous system, were detected in the cerebrospinal fluid of PTSD patients [49]. Noradrenaline is considered as one of the important mediators of central and peripheral autonomic stress response and has an important role in the regulation process of emotional memory [50]. It was also shown that high levels of noradrenalinefof the PTSD of the PTSD in urine positively correlate with the symptoms of PTSD [51]. In addition, the increased levels of dopamine, another mediator of the sympathetic nervous system and precursor of noradrenaline, were found in the blood and body fluids of PTSD-affected subjects [51-53].

There are several data indicating assumption that functional abnormalities in neuroendocrine system detected in PTSD patients are conditioned by hereditary factors [54]. Thus, as it

follows from table 2, PTSD is associated with the genetic mutations in a number of genes encoding neurotransmitters and hormones, their biosynthesis enzymes, receptors and transporters. Interestingly, 6 of the candidate genes for PTSD showed in the table 1 belong to the dopamine system. A positive association between the risk for development PTSD and TaqIA polymorphism of the dopamine D2 receptor gene was found [55]. Also, positive association was revealed between tandem repeat polymorphism of dopamine transporter gene and PTSD [56] as well as between dopamine D4 transporter gene long allele and severity of PTSD symptoms [57].

The γ-3 subunit of γ-aminobutyric acid, another mediator of nervous system, has also been studied in PSTD patients. Patients heterozygous for this gene have a higher probability of developing somatic symptoms of PTSD, sleeping disturbances, fair and depression than homozygous patients [58]. The studies of serotonin transporter gene showed that PTSD patients carrying one or two short alleles of this gene have a higher level of depression and suicide compared to carriers of long allele, which has more transcriptional power [59, 60]. The association of the serotonin transporter repeat polymorphism with PTSD was also described [61-63]. Interestingly, recent study of 200 individuals from 12 multigenerational families survived 1998 Spitak earthquake in Armenia demonstrated that PTSD is developing in those individuals, who carry mutations of tryptophan hydroxylase 1 and 2, the rate-limiting enzyme of serotonin biosynthesis [64].

Candidate gene	Chromosomal mapping	Source
Dopamine D2 receptor	11q23	[22, 55, 65]
Dopamine D4 receptor	11p15.5	[57]
Dopamine transporter type 1	5p15.3	[56, 66]
Serotonin transporter	17q11	[10, 60, 63, 67- 71]
Serotonin type-2A receptor	13q14-q21	[68]
Brain-derived neurotrophic factor	11p13	[72]
Neuropeptide Y	7p15.1	[73]
Glucocorticoid receptor	5q31.3	[74]
Dopamine beta-hydroxylase	9q34	[75]
Cannabinoid receptor	6q14-q15	[76]
γ-aminobutyric acid receptor (subunit α-2)	4p12	[77]
Catechol-O-methyltransferase	22q11	[78]
Tryptophan hydroxylase 1 Tryptophan hydroxylase 2	11p15.3-p.14 12q21.1	[64]

Table 2. PTSD-related changes in the neuroendocrine system

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3. Immune system alterations in PTSD

Promising studies suggest the involvement of alterations in the immune status [48, 79-86], particularly low-grade inflammatory reactions, in the pathogenesis of PTSD [87-97]. Thus, PTSD patients are characterized by hyperactivation of lymphocytes [80] and increased levels of lipopolysaccharide (LPS)-stimulated expression of interleukin (IL)-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ in immunocompetent cells [81, 82]. Segman et al detected over-expression of immune response-related genes in monocytes of PTSD-affected subjects [85]. Also, in chronic PTSD patients, as compared to norm, a decreased number of T-killer cells ($CD8^+$) [98, 99] and an increase number of T-helper cells ($CD4^+$) [98, 100] has been shown, whereas in PTSD patients immediately after a traumatic event a decreased number of T-helper cells was detected [99]. A number of experimental data indicates that natural killer cells' cytotoxicity in PTSD is lower than in norm [97, 99, 101-104], while the total number or these cells, as well as a number of $CD16^+$ and $CD56^+$ cells in their total population is higher than in norm [99, 104]. At the same time some studies show that natural killer cells' cytotoxicity in PTSD patients is higher than in healthy subjects [105, 106]. The analysis of the above mentioned data revealed altered cell-mediated immunity in PTSD patients and demonstrates that depending on traumatic event, duration and stage of the illness, these alterations may be either under- or over-represented [97, 107].

3.1. Cytokine network in PTSD

A number of studies have demonstrated changes in a functional state of cytokines and their receptors, important mediators and regulators of the immune response in PTSD-affected subjects. Here the increased blood levels of proinflammatory cytokines (e.g. IL-1β, IL-6, TNF-α, INF-γ) and decreased levels of anti-inflammatory cytokines (e.g. IL-4) are detected in chronic PTSD patients indicating the involvement of low-grade systemic inflammatory reactions in PTSD pathogenesis (table 3).

In our own study the levels of proinflammatory and chemotactic cytokines IL-1β, IL-6, TNF-α, IL-8 and MCP-1 in the blood serum of chronic PTSD patients (combat veterans) and age- and sex-matched healthy subjects (HS; a control group) were determined using enzyme-linked immunosorbent assay (ELISA). Assessment of possible correlation of the above mentioned parameters with each other and with the expression of PTSD clinical symptoms was also performed. The latest were evaluated using Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID PTSD module) [112] and Clinician-Administered PTSD Scale (CAPS) [113]. In particular, we assessed correlation between the levels of cytokines and the degree of expression of such PTSD clinical symptoms as persistent re-experiencing of the traumatic event (B cluster), persistent avoidance of stimuli associated with the trauma and emotional numbing (C cluster); persistent symptoms of increasing arousal (D cluster) [2]. In table 4 brief descriptions of the study groups is given. Table 5 demonstrates the individual symptom clusters (B, C, and D criteria), and total CAPS scores of PTSD-affected subjects involved in our study.

Chronic PTSD patients: group description	Changes in the blood levels of cytokines as compared to norm*	Source
Accidents survivors (n=13)	↑IL-1β, ↑IL-6, ↑TNF-α	[89]
Accident survivors (n=86)	↑IL-1β	[46]
Accidents survivors (n=14)	↑IL-1β, ↑TNF-α, ↓IL-4	[93]
Bosnian refugees (n=12)	↑IL-6	[108]
Combat veterans (n=19)	↑IL-1β, ↑IL-6, ↑TNF-α	[87]
Combat veterans (n=11)	↑IL-6, ↑TNF-α	[91]
Individuals abused in childhood (n=30)	↑INF-γ	[109]
Individuals abused in childhood (n=177)	↑TNF-α , ↓IL-4	[110]
Individuals exposed to different traumatic events (n=60)	↓IL-4	[97]
Individuals exposed to intimate partner violence (n=62)	↑IL-6, ↑TNF-α, ↑INF-γ	[111]

* - ↑ - above the norm; ↓ - below the norm.

Table 3. Changes in the blood levels of some cytokines in chronic PTSD patients

Data statistics include nonparametric Mann-Whitney U-test and correlation analysis with calculation of Spearman's rank correlation coefficient (Rs). Parts of this study have been published [114, 115].

The results obtained indicated that PTSD, as compared to norm, is characterized by increased levels of the mentioned above cytokines (Table 6), which is consistent with reports by other research groups (Table 3) [46, 87, 89, 91, 93, 108, 110, 111].

A significant correlation between the levels of IL-1β and IL-6 ($Rs=0.45$; $p<0.003$), as well as between IL-1β and MCP-1 ($Rs=0.3$; $p<0.03$) in PTSD patients was revealed, whereas no significant correlation between the levels of cytokines was observed in control group. Also, a significant positive correlation of IL-1β and IL-6 blood levels with PTSD symptoms within B, C and D criteria (CAPS scores) was detected. Thus, levels of IL-1β positively correlated with B frequency ($Rs=0.004$, $p=0.007$), C frequency, intensity, and frequency + intensity ($Rs=0.4$, $p=0.009$; $Rs=0.30$, $p=0.035$, $r=0.36$, $p<0.02$, respectively), frequency of B, C and D ($Rs=0.37$, $p<0.02$), total intensity of B, C and D ($Rs=0.3$, $p<0.048$) and total frequency + intensity of B, C and D ($Rs=0.3$, $p<0.03$). Blood levels of IL-6 positively correlated with cluster B frequency ($Rs=0.3$, $p=0.048$).

Our data provides further evidence on the association of chronic inflammation with PTSD and clearly demonstrates the interrelation between the expression of PTSD symptoms and inflammatory reactions. Alterations in the immune response in PTSD accompanied by low-grade systemic inflammation aggravate disease course and severity and contribute to development of complications. Thus, PTSD is often associated with autoimmune and

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inflammatory disorders such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. Patients with PTSD are at a higher risk for diabetes mellitus and cardiovascular diseases (atherosclerosis, myocardial infarction) [116-123]. It is interesting that in peridontitis patients with PTSD higher expression of inflammatory processes was obtained than in those peridontitis patients, who were not affected by PTSD [88].

Study group	PTSD	HS
Total number (male/female)	120 (116/4)	80 (76/4)
Mean age (M±SD)	42 ± 11.3	39 ± 9.1
[Cortisol]* (M±SD), ng/ml	124 ± 47	145 ± 55
[DHEA]* (M±SD), ng/ml	13 ± 7	10 ± 5
[DHEA-sulfate]* (M±SD), µg/ml	1.8 ± 0.9	1.0 ± 0.5

* - measured in the blood serum

Table 4. Brief description of the study groups

Symptom clusters	Parameters	PTSD patients scores
B cluster	Frequency (0-20)	11.8±3.98
	Intensity (0-20)	11.6±3.46
	Frequency + Intensity (0-40)	23.4±7.02
C cluster	Frequency (0-28)	16.4±5.10
	Intensity (0-28)	14.8±4.96
	Frequency + Intensity (0-56)	31.2±9.85
D cluster	Frequency (0-20)	13.5±3.07
	Intensity (0-20)	12.2±2.52
	Frequency + Intensity (0-40)	25.7±5.30
B+C+D (Total)	Frequency (0-68)	41.7±9.85
	Intensity (0-68)	38.6±9.18
	Frequency + Intensity (0-136)	80.3±18.50

Table 5. The individual symptom clusters (B, C, and D criteria), total and overall CAPS scores (M±SD) of PTSD-affected subjects (Score ranges are indicated in parenthesis)

Study group	Cytokine	Level (M ± SD), pg/ml	P =
PTSD	IL-1β	8.2 ± 1.0	0.002
HS		5.1 ± 0.7	
PTSD	IL-6	19.0 ± 2.5	0.025
HS		16.0 ± 2.3	
PTSD	TNF-α	12.0 ± 1.6	0.049
HS		10.8 ± 1.4	
PTSD	IL-8	11.5 ± 1.5	0.022
HS		10.1 ± 1.3	
PTSD	MCP-1	223.3 ± 30.6	0.030
HS		187.2 ± 25.5	

Table 6. Comparative analysis of the blood serum levels of proinflammatory and chemotactic cytokines in patients with PTSD and HS

The pathological mechanisms of the development of inflammatory reactions in PTSD are not clear. However, it is obvious that neuroendocrine and immune impairments in PTSD are interrelated. It is well-established fact that the immune system functional activity is regulated by neurotransmitters and hormones, particularly those related to HPA axis and SAS. On the other hand, immune system mediators and their receptors on the immunocompetent cells may regulate the neuroendocrine system. In normal physiological conditions the immune, endocrine and nervous systems maintain homeostasis by controlling each other, thus developing adequate stress response [79, 124]. Changes in neuro-endocrine-immune interactions (influenced by either environmental or genetic factors) may result to abnormal response to stress and generation of PTSD. On the other hand, the action of cytokines, mediators of inflammation, is tightly coupled with physiological and pathophysiological reactions of the organism, and their important role is to coordinate the efforts of the immune, endocrine and nervous systems during the stress response [125-128]. This may represent one of the possible mechanisms responsible for increased cytokines levels and development of chronic inflammatory reactions in PTSD, the disease characterized by neuroimmune and endocrine alterations [82, 86, 129]. It connection with this it has to be also mentioned that a number of recent clinical and experimental data suggests the implication of low-grade systemic inflammatory reactions accompanied by increase in cytokines levels in pathogenesis of many psychiatric disorders [130-132].

3.2. The complement system in PTSD

The complement system is major effector of the immune response, which acts on the interface of innate and adaptive immunity, and is a key component and trigger of many immunoregulatory mechanisms. Activation of the complement generates opsonins, anaphylatoxins, and chemotaxins, mediators of inflammation and apoptosis (Figure 1)

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[133-135]. Changes in the functional activity of the complement cascade contribute to the pathology of many human diseases [136-138], including mental disorders [139-144], and are also detected during physiological stress [145-146]. The alterations in the complement cascade have been considered as indicator of the implication of inflammatory component in disease etiology, pathogenesis and/or progression [136-138].

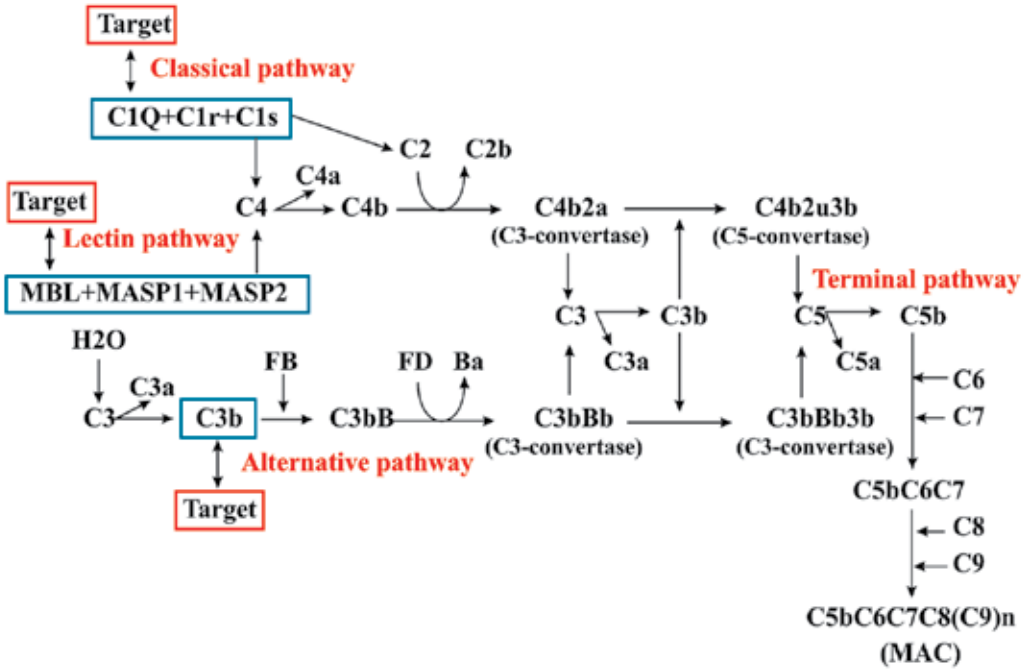

Figure 1. Complement activation pathways; C1Q, C1r, C1s – subunits of the complement C1 component; MBL - mannan-binding lectin; MASP1 - MBL-associated serine peptidase 1; MASP2 - MBL-associated serine peptidase 2; FD - factor D; FB - factor B; MAC – membrane attack complex.

The complement system with its central position in innate and adaptive immunity mediates a variety of effector functions. It consists of more than 30 circulating proteins, cell surface receptor and regulator proteins. It is a complex cascade involving proteolytic cleavage of serum glycoproteins often activated by cell receptors. This cascade ultimately results in induction of the antibody responses, inflammation, phagocyte chemotaxis, and opsonization of apoptotic and necrotic cells, facilitating their recognition, clearance, and lysis. Complement exhibits three activation pathways - classical, alternative, and lectin, initiated via separate mechanisms, and a single terminal pathway that results in a formation of the membrane attack complex (Figure 1) and subsequent cell lysis [133-135]. During the past decades it has become evident that dysfunction of complement contributes to the pathology of many human diseases [136-138], including mental disorders (schizophrenia, Alzheimer's disease, Huntington's and Pick's diseases) [139-142], and is also detected during physiological stress [145-146]. While, as it was already mentioned, PTSD-affected subjects showed a low-grade

systemic proinflammatory state, the complement system in PTSD has been never studied before.

In our study we assessed the functional activity of the complement cascade in PTSD by determining total hemolytic activities of its classical and alternative pathways, and hemolytic activities of its individual components, C1, C2, C3, C4, factor B and factor D, in the blood serum of chronic PTSD patients (combat veterans) and HS (tables 4, 5). C1, C2 and C4 are main components of the classical pathway, factor B and factor D are essential components of the alternative pathway, and C3 is the initial point for the alternative pathway and a converge point of all three complement activation pathways, starting up for the terminal pathway (Figure 1) [133-135]. In addition, correlation study between all measured parameters was also performed. Hemolytic activities of the complement classical and alternative pathways (CH50 and AH50, respectively) and of the complement components C1 (C1H50), C2 (C2H50), C3 (C3H50), C4 (C4H50), factor B (fBH50), and factor D (fDH50) in the blood serum of PTSD-affected and healthy subjects were measured by application of the earlier developed methods [147, 148]. Data was analyzed by Student's unpaired two-tailed t-test and Pearson's correlation analysis including calculation of relevant correlation coefficient (r). Parts of this study have been published [149-152].

The results obtained are presented in table 7. According to the results obtained, mean values of serum CH50, C1H50, C2H50 and C4H50 in PTSD patients were significantly 2.1, 1.34, 1.2 and 1.6 times significantly higher than in case of HS ($p<0.05$). On the contrary, mean values of serum C3H50, AH50, fBH50, and fDH50 in PTSD patients were 1.5, 1.7, 1.6, and 2.3 times significantly lower as compared to HS ($p<0.05$). Correlation analysis also demonstrated that in PTSD affected subjects C1H50 is significantly correlated with C2H50 ($r=-0.375$, $p<0.04$), C3H50 is significantly correlated with C1H50, C2H50 and C4H50 and AH50 ($r=0.53$, $p<0.037$; $r=0.72$, $p=0.002$; $r=0.5$, $p=0.05$; $r=0.57$, $p=0.027$, respectively). No significant correlation between the above-mentioned parameters was detected in the HS group ($p>0.05$).

Hemolytic activity, U/ml*	PTSD (M ± SD)	HS (M ± SD)	P =
CH50	375.00 ± 164.40	176.00 ± 88.50	0.0002
C1H50	92.21 ± 52.83	68.80 ± 37.39	0.0400
C2H50	67.60 ± 35.10	58.80 ± 8.80	0.0450
C3H50	37.57 ± 16.26	55.92 ± 28.60	0.0300
C4H50	60.10 ± 28.42	36.64 ± 20.31	0.0300
AH50	52.30 ± 18.17	87.60 ± 9.80	0.0001
fBH50	40.80 ± 14.30	65.2 ± 34.1	0.0200
fBH50	71.70 ± 15.98	163.70 ± 70.58	0.0010

* - one unit (U) of hemolytic activity is defined as an amount of serum that causes a 50% hemolysis of erythrocytes in a reaction mixture.

Table 7. Functional state of the complement system in PTSD patients and HS

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The results obtained in our study clearly demonstrated that pathogenesis of PTSD is characterized by complement dysfunction including hyperactivation state of the complement classical pathway and hypoactivation state of the complement alternative pathway. The alternative pathway of complement is activated following spontaneous hydrolysis of the thioester bond of native C3, resulting into binding of factor B, which is cleaved by factor D, generating the efficient alternative pathway C3 convertase C3bBb. Multifunctional complement protein C3 is the initial point of the alternative pathway, and, at the same time, a converge point of all three complement activation pathways, i.e. starting point for the terminal pathway [93, 135, 153]. Hypoactivation state of the alternative pathway together with decreased activity of the complement C3 component, detected in PTSD affected subjects, probably reflects depletion of the C3 component due to its overutilization through the terminal pathway. This suggestion is convenient with correlation data indicating positive correlation between CH50 and C3H50 and absence of any correlation between AH50 and fBH50, and AH50 and fDH50 in PTSD affected subjects. Thus, it is obvious that the alternative pathway in PTSD is suppressed on the initial stage of its activation, and that PTSD is also characterized by overactivated terminal complement pathway. On the other hand, absence of correlation between AH50 and CH50 suggests that alterations in activities of the classical and the alternative complement pathways in PTSD are not interdependent.

As it was mentioned above, alterations in the complement cascade have been considered as indicator of the implication of inflammatory component in disease etiology, pathogenesis and/or progression [136-138]. Our study demonstrates that PTSD is associated with dysfunction of the complement system, and reveals the altered chains of the complement cascade. The results obtained provide further evidence on the involvement of the inflammatory component in pathogenesis of PTSD. Here we hypothesize that neuroendocrine mechanisms related to PTSD modulating the immune function might affect the initial steps in the inflammatory cascade and thus influence alterations in the functional activity of the major mediator of the inflammatory response, the complement system. However, to address molecular mechanisms responsible for the complement dysfunction in PTSD as well as their role in PTSD pathogenesis further studies are needed.

3.3. Immune complexes in PTSD

Formation of immune complexes (IC) is a normal physiological reaction of organism to foreign or autoantigen. IC may interact with both humoral and cellular components of the immune recognition system, activate the complement cascade, and thus affect the immune response on multiple levels [154-156]. In healthy conditions IC are easily eliminating from circulation through complement deposition, followed by their opsonization, phagocytosis, and further processing by proteases [154, 156-158]. In pathologic conditions inappropriate clearance or deposition of IC result in increased levels of IC in circulation. Circulating IC may deposit in endothelial or vascular structures provoking prolonged inflammatory response by permanent activation of the complement cascade through the classical pathway, generation of cytotoxic agents and tissue damage [159-163]. Deposition of IC is a prominent feature of many diseases [162-164] including those characterized by low-grade systemic in-

flammation, such as schizophrenia [144], diabetes mellitus [165, 166], ischemic and hemorrhagic stroke [167-169].

In our own study we, for the first time, determined total levels of IC as well as the levels of IC containing activation products of the complement system, C1q- and C3d-IC, in the blood serum of chronic PTSD patients (combat veterans) and HS. Brief characteristic of study groups is given in tables 3, 4. Total levels of IC were measured by a previously published spectrophotometric method and expressed in absorbency units at 280 nm (A_{280}) [167]; C1q- and C3d-IC were measured by ELISA. Data was analyzed by Student's unpaired two-tailed t-test and Pearson's correlation analysis including calculation of relevant correlation coefficient (r). Parts of this study have been published [149, 150, 170].

According to the results obtained, PTSD-patients comparing to HS are characterized by significantly increased serum levels of total IC as well as C1q- and C3d-IC. Thus, the mean level of total IC in PTSD patients was 1.5 times higher than in HS (p=0.0055) and the levels of C1q-IC, and C3d-IC were 1.7 (p=0.024) and 1.6 times (p=0.0004), respectively, higher as compared to HS. The results obtained are summarized in table 8.

[IC], (M±SD)	Study group		P =
	PTSD	HS	
[Total IC], A_{280}	0.18 ± 0.1	0.12 ± 0.03	0.0055
[C1q-IC], μg/ml (M±SD)	44.6 ± 37.67	26.28 ± 16.33	0.024
[C3d-IC], μg/ml (M±SD)	29.75 ± 21.91	18.67 ± 8.22	0.0004

Table 8. Serum levels of the total IC, C1q-IC and C3d-IC in PTSD patients and HS

In addition, a significant positive correlation between the levels of C1q- and C3d-IC (r=0.32; p<0.03) was detected in PTSD patients affected subjects. Moreover, in patients with PTSD we also revealed a significant positive correlation between the total levels of IC and hemolytic activity of the classical complement pathway. This finding indicates that increased total levels of IC in circulation may be responsible for hyperactivation of the classical complement cascade detected in PTSD [149-152, 170].

The increased blood levels of C1q-IC in PTSD provide further evidence for this suggestion. C1q-IC contain C1q subunit of the complement protein C1, and binding of IC to C1q initiates activation of the classical complement cascade (Figure 1) [133-135].

C3d-IC contain activation cleavage products of the complement C3 protein, opsonins C3b, iC3b and C3dg. These entire products contain "d"-terminal fragment of the C3 polypeptide chain. In healthy conditions C3d-IC are eliminated from the blood through interaction with the complement receptors on monocytes, neutrophils and erythrocytes. Monocytes and neutrophils subject C3d-IC to phagocytosis, and erythrocytes transfer them to liver and spleen for further phagocytosis by macrophages. Increased blood levels of C3d-IC suggest about al-

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terations in mechanisms responsible for their recognition and clearance by the above mentioned cells. High levels of C3d-IC result in hyper-production of antibodies, because binding of C3d-IC to type-2 complement receptors (CR2) on the surface of B-lymphocytes induces the production of immunoglobulins by these cells [154, 156-158]. Therefore, our results indicate that PTSD is characterized by altered mechanisms of IC recognition and clearance, which may be responsible for the increased classical pathway functional activity, chronic activation of the immune system and systemic inflammation.

3.4. Interrelation between inflammatory response, apoptosis and synaptic plasticity in PTSD

As it was already mentioned, the molecular pathomechanisms responsible for development of inflammatory reactions in PTSD are yet unclear, which limits the progress in development of the efficient measures of PTSD rehabilitation therapy and prevention of its complications. On the other hand, it is known that apoptosis plays an important role in down-regulation of the inflammatory response by reducing the lifespan of activated immunocompetent cells [171-173]. Therefore, we proposed that one of the factors contributing to PTSD-associated inflammation may be apoptotic dysfunction as it was observed in case of other disorders like familial Mediterranean fever [174], inflammatory bowel disease [175], systemic inflammatory response syndrome [176], pulmonary hemorrhage or endotoxemia [177], etc.

On the third though, apoptosis is considered as the important regulator of synaptic plasticity. Apoptotic alterations have a significant input in synaptic dysfunction and lead to changes in structural and functional integrity of neuronal circuits [178-180]. Therefore, apoptosis may be also responsible for altered synaptic plasticity in PTSD [181] resulting in cognitive impairments and development of depressions in PTSD affected subjects [182-184].

To check our hypotheses, in the blood serum of patients with PTSD, in comparison to HS the levels of marker proteins for apoptosis and synaptic plasticity, annexin-A5 [185] and complexin-2 [186], respectively, and the inflammatory marker, TNF-α, were determined by ELISA. The analysis of correlation between these parameters was performed. Brief characteristic of study groups is given in tables 4, 5. Data statistics include nonparametric Mann-Whitney U-test and correlation analysis with calculation of Spearman's rank correlation coefficient (Rs). The results presented below have not been published yet.

According to the results obtained, the levels of both annexin-A5 and complexin-2 in PTSD patients were significantly 2.34 ($p=0.0001$) and 1.21 ($p=0.03$) times, respectively, lower than in case of HS (table 9). In addition, a significant positive correlation between the levels of annexin-A5 and complexin-2 ($Rs=0.38$, $p=0.045$), on the one hand, and a significant negative correlation between the levels of annexin-A5 and the increased levels of TNF-α ($Rs= -0.35$, $p=0.047$), on the other hand, were detected in PTSD.

No statistical significant correlation was observed between these parameters in case of HS.

Study group	[Annexin-A5], ng/ml	P =	[Complexin-2], pg/ml	P =
PTSD	0.82 ± 0.70	0.0001	121.5 ± 41.20	0.03
HS	1.92 ± 1.05		146.9 ± 56.64	

Table 9. The levels of annexin A5 and complexin-2 (M ± SD) in PTSD patients and HS

Our results demonstrated that PTSD is characterized by the decreased blood levels of the apoptotic marker circulating annexin A5 indicating association of apoptosis hypofunction with this disorder.

On the base of the results obtained we suggest that PTSD is characterized by low rate of apoptosis associated with the defects in synaptic plasticity and that anomalous apoptosis may also represent one of the factors responsible for development of PTSD-associated chronic inflammation. This suggestion is confirmed by recent findings indicating the increased levels of leukocytes in the blood of chronic PTSD patients [48, 93, 94].

4. Conclusion

The results presented in this chapter provide evidence on implication of altered immune response, particularly low-grade systemic inflammation, in pathogenesis of PTSD.

In particular, we demonstrated that chronic PTSD is characterized by increased blood levels of proinflammatory and chemotactic cytokines, IL-1β, IL-6, TNF-α and MCP-1, IL-8, respectively. Here, the increased levels of IL-1β and IL-6 positively correlate with the degree of expression of clinically significant symptoms of this disease, which indicate that these cytokines may be considered as new therapeutic targets for PTSD treatment. In addition, we demonstrated that chronic PTSD is characterized by altered mechanisms of IC recognition and clearance resulting in the increased levels of total IC, as well as C1q-IC and C3d-IC in circulation. Furthermore, our results showed that chronic PTSD is characterized by alterations in functional activity of the complement pathways including hyperactivation state of the classical and terminal pathways, hypoactivation state of the alternative pathway and deficiency of the C3 complement protein. Here, the data obtained suggests that hyperactivation of the classical complement pathway is induced by the increased levels of IC, particularly C1q-IC, in circulation. Regarding the alternative pathway, our results clearly demonstrated that it is suppressed at the initial stage of activation and that decreased activity of this pathway in PTSD is stipulated by decreased activities of its components, factor B and factor D, and deficiency of the protein C3, a key component of the complement cascade.

In summery, we concluded that changes in functional activities of the proinflammatory and chemotactic cytokines and complement cascade, as well as disturbances in the IC recognition and clearance processes are implicated in pathogenesis of chronic PTSD.

Another important conclusion that can be drawn from the results of our study is that pathogenesis of chronic PTSD is characterized by low rate of apoptosis associated with the defects

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in synaptic plasticity, and that anomalous apoptosis may represent one of the factors responsible for development of PTSD-associated chronic inflammation.

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Chapter 6

Understanding the Causes of Reduced Startle Reactivity in Stress-Related Mental Disorders

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Additional information is available at the end of the chapter

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1. Introduction

Many questions have plagued the study of the etiology and subsequent treatment of mental illness. In part, it is simply because, as far as we know, some mental illnesses are somewhat unique to the human condition. Moreover, clinical studies have produced many different results concerning potential biomarkers for conditions such as post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). In this chapter, we review how we approached modeling a specific behavioral condition, suppression of the startle reflex, by examining whether one of two commonly associated peripheral biomarkers of anxiety and depression could potentially cause this rather specific symptom. The two peripheral systems under investigation were the hypothalamic-pituitary-adrenal (HPA) axis and the peripheral pro-inflammatory immune response, both of which have been implicated as a vulnerability factor, causal factor, or resultant (perpetuating) effect of PTSD and MDD.

Our general theory is that peripheral endocrine and immune signals, measured to be abnormal in patients with either PTSD or MDD (as well as other mental disorders), are actually perpetuating the behavioral features of these disorders. At the same time, if an individual has an immunosensitivity or has an overactive adrenal gland, s/he would be more likely to experience some of the symptoms associated with one of the particular mental illnesses. This may then lead the brain to compensate for those peripheral abnormalities, but, at the same time, cause other imbalances, which lead to the experience of a decline into mental illness. Thus, treating these peripheral markers as part of the "mental" disorder may be quite beneficial in normalizing certain aspects of the diagnosed abnormal behavior.

2. The startle reflex and mental health

2.1. The startle reflex as an assessment tool

One of the major impediments to the mechanistic study of mental illness is establishing analogs of the abnormal behaviors expressed in humans in animal models, especially in sub-primate species. This has led some to adopt reflex-based measures such that the face and construct validity of the behavior change can be readily translated between the model and patient populations. Consequently, a popular measures for the study of anxiety disorders has been the potentiation of the startle reflex; however, there is growing evidence that a dampening of the startle response may be indicative of changes in physiology that underlie different mental disorders.

The startle reflex comprises a 3-synaptic sensory-motor neuronal pathway that serves as a defensive behavioral response to abrupt, usually intense, stimuli. The acoustic startle response (ASR) is the most commonly used form for studying this reflex. As shown in Figure 1, the primary ASR circuit begins with neurons in the cochlear nerve, transmitting the representation of the acoustic stimulus from the cochlea of the inner ear to the cochlear nucleus (in the brainstem). Efferent pathways from the cochlear nucleus project to the nucleus reticularis pontis caudalis (PnC), in the pons, forming the second synapse in this reflex arc. The third synapse forms from the efferent projections from the PnC to various motor nuclei, through the recticulospinal spinal tracts to the muscles of the torso [1] and the muscles enervated by the facial nerve. These muscle enervations create a rapid cascade of near-immediate behavioral responses to abrupt acoustic stimuli, ranging from less than 10 ms to approximately 50 ms.

The ASR is modulated by several afferent connections originating from higher brain areas (midbrain, limbic, and cortical nuclei). At the level of the PnC, there are several inputs that can either enhance or inhibit the magnitude of an elicited ASR. In the area of fear and anxiety, the central amygdala and bed nucleus of the stria terminalis (BNST) are considered the 2 major excitatory modulation structures on this reflex [2]. Some have proposed that the BNST is the origin of anxiety-like behaviors whereas the nuclei of the amygdala are the origin of acute fear responses and explicit fear-learning [3, 4]. The amygdala is predominately associated with causing classically conditioned fear-potentiated ASRs [5], and, in fact, has been specifically shown not to have a role in startle inhibition, at least via a learned conditioned inhibitor [6]. On the other hand, the process known as pre-pulse inhibition of the startle reflex (PPI) has elucidated neural pathways that can inhibit the expression of the ASR. For instance, the substantial nigra pars retriculata (SNR), pedunculopontine tegmentum (PPT) and laterodorsal tegmental nuclei (LDT) have inhibitory influence upon the PnC, thus reducing the measured ASR [7-10]. These three mid-brain nuclei (inhibitory) receive projections from various forebrain areas, including the amygdala, BNST, and medial prefrontal cortex (mPFC). Thus, limbic system modulation of the ASR can occur through direct enervation of the PnC (excitatory) or indirect enervation through mid-brain nuclei.

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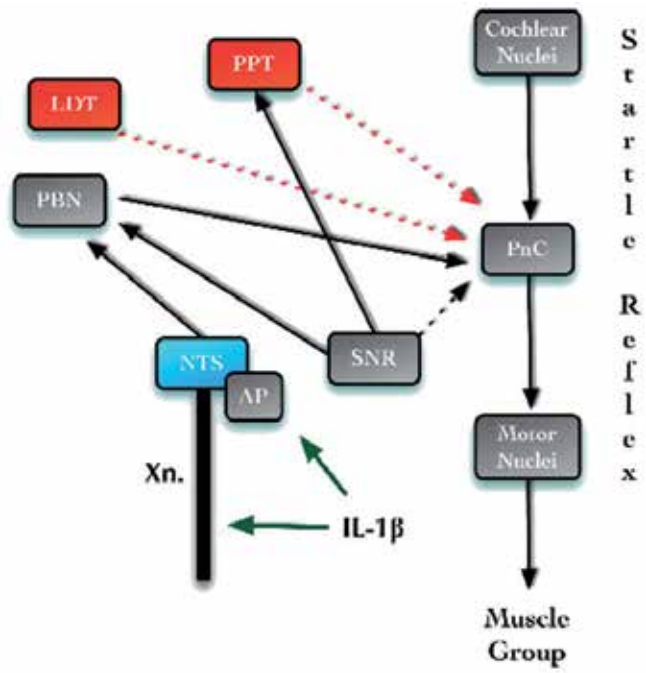

Figure 1. There are several nuclei within the midbrain/brainstem area that can directly modulate the intrinsic ASR circuit at the level of the nucleus reticularis pontis caudalis (PnC). Dashed red lines represent cholinergic inhibitory influences from the laterodorsal tegmental nuclei (LDT) and pedunculopontine tegmentum (PPT). Dashed black lines represent inhibitory GABAergic projections from the substantial nigra pars reticulata (SNR). A solid line from the parabrachial nucleus (PBN) is an example of a direct excitatory input to the PnC.

2.2. Abnormalities in the expression of the startle reflex in mental disorders

Over all other mental disorders, PTSD is associated with changes in the startle reflex. Commonly associated with exaggerated startle responses [11-14], higher or exaggerated startle reflex responses are a criteria symptom for the diagnosis of PTSD [15]. However, recent evidence suggests that this may not always be the case. In fact, others have reviewed the literature and found there are a significant number of reports where the startle responses in PTSD patients are not exaggerated [16]. More extreme, there are reports, albeit limited, where patients diagnosed with PTSD appeared to have blunted motor reflex responses to an acoustic stimulus [17, 18]. These populations had distinctive qualities that were different than those studies that had found enhanced startle reactivity in their PTSD patients. First, the one study was exclusively female [18] and the other had a majority of female subjects [17], suggesting there may be a sex difference in the presentation of ASR in females as a result of experiencing trauma. However, others have reported enhanced startle responses in a different population of women diagnosed with PTSD following automobile accidents [19]. Thus, a second distinction between the two studies that observed suppressed startle reactions, which should be considered, is that the trauma was specifically associated with being the target of violence [17, 18]. Although women with a PTSD diagnosis stemming from a prior rape have

not always exhibited blunted startle responses [20], this discrepancy may be due to individual differences and/or methodological differences in being sensitive to such changes, as some have reported laterality effects in PTSD patients, notably of those having been raped in the past [21]. A third quality of at least one of these two reports is that the subjects also exhibited symptoms associated with major depressive disorder [18]. This suggests stressful experiences may not cause a uniform change in sensory reactivity, and the expression of the coping response to the trauma may have psychophysiological ramifications that are quite different, both in terms of effects upon sensory-motor responding to acoustic stimuli as well as the full expression of symptoms.

There is evidence that symptoms associated with depression may also include a blunted reaction to acoustic stimuli. Patients designated as "depressed", having either a diagnosis of MDD or a significantly higher score on the Beck Depression Inventory (with or without additional neurological conditions), have been reported to exhibit blunted reactivity to acoustic stimuli, either with or without manipulations of affect [22-26]. Similarly, there is also evidence that bipolar disorder (BPD), the occurrence of at least one manic or mixed manic episode over the course of a patient's lifetime, is characterized by blunted startle reactions as well, even during periods of remission [27]. A study by Carroll and colleagues found patients suffering from BPD exhibit attenuated baseline startle, most notably in those having experienced mixed episodes, not pure mania [28]. These data suggest there is a neurobiology of startle suppression that may provide critical insight to the underlying biological conditions that cause areas of the brain to improperly process information, in this case sensory-motor responses.

2.3. Animal models utilizing stress to dampen startle reactivity

Across the studies that have documented reductions in the expression of the startle reflex in rodents, the common-most feature is that the magnitude of the response is dampened following exposure to a stressor manipulation. Reduced startle amplitudes have been documented in rats following: repeated 20 min restraint [29]; inescapable tailshock [30-32]; predator exposure coupled with an intraperitoneal injection [33]; immune-challenge [34, 35], and a single session of footshocks [36]. Interestingly, despite some differences in methodology, inescapable tailshock [30], inescapable footshock [36], and predator exposure with injection [33], all showed reduction in ASR measurements that could *not* be attributable to enhanced habituation to the acoustic stimuli. Yet, studies utilizing inescapable tailshock (in females) *have* established that exposure to the stressor condition causes a change in startle responsivity (the magnitude of the measured startle responses), not startle sensitivity (the threshold to elicit a certain percentage of startle responses). Thresholds for eliciting ASRs are not increased in the shocked females; instead, the magnitudes of the elicited startle responses are lower [31, 32]. This suggests, at least for the female stress model, that the presumed increased inhibition upon the activity in the intrinsic ASR circuit is occurring through the motor response aspect of the reflex arc. The muscles are simply not as mobilized when this condition is induced. This model condition has been termed by some *stress-induced startle suppression* [32, 34].

There are significant differences in the temporal characteristics of these different startle-suppression models in rodents. Inescapable tailshock causes a reduction in startle magnitude in female rats that is evident hours within exposure [31, 32], possibly lasting up to a day later, when the bouts of shock are expanded to a few consecutive days [30]. The footshock-in-

duced suppression of startle reactivity is evident 4 h following stressor exposure [36]. The immune-challenge models parallel these stressor manipulations by causing reductions in startle reactivity within a couple hours of administration of the challenge [34, 35]. Thus, one interpretation of these data is that painful stressors are causing changes in the peripheral immune system, which, in turn, dampen startle reactivity during the time of their activity [34], on the range of hours. Following this logic, when females were tracked 4 and 8 days following tailshock, reductions in startle reactivity in the stressor-exposed rats did not reach statistical significance [30]. In contrast, the predator-exposure + injection model shows immediate suppression following the stressor exposure, which continues to be present 1 week later [33]. In addition, it is evident both under dark and light conditions [33], suggesting the change in the startle response is not occurring due to a change in reactivity to other stimuli that are known to modulate startle reactivity, such as light-enhanced startle [37]. Thus, this observance suggests that changes in ASR magnitude may be extended beyond the acute effects of stressor exposure that could be attributed to the short-term effects of immune signaling that would be in response to the injection (or possibly even shock).

3. Peripheral mechanisms of reduced startle reactivity

3.1. Hypothalamic-Pituitary Adrenal (HPA)–axis

Two interrelated mechanisms have been proposed as potential causes of startle suppression, the first being glucocorticoid hormone reception. Adamec and colleagues showed the reduction of startle magnitudes following combined cat exposure and saline injection could be blocked by substituting the saline injection with the glucocorticoid receptor antagonists RU-486 [33]. We subsequently tried to induce the effect in our female rats by administering the synthetic glucocorticoid agonist, dexamethasone. Startle responses were assessed 2 and 4 h following dexamethasone administration. As shown in Figure 2, the dexamethasone did not appreciably change the magnitude of the elicited ASRs, nor did it affect the number of ASRs elicited (data not shown). These findings suggest that the reception of corticosterone at the glucorticoid receptor is not sufficient to reduce ASR magnitudes. One possibility is that RU-486 blocked the suppressed startle, in that model system, via a non-glucocorticoid mechanism, for example via progesterone receptor antagonism. A connection to progesterone will be discussed further below as it pertains to a pro-inflammatory response mechanism, in contrast to an anti-inflammatory glucocorticoid response, but this finding is supported by previous work that shows elevations in circulating corticosterone are not necessary for corticotrophin releasing hormone to increase ASR magnitudes, despite stimulating increased activity in the HPA-axis [38]. Likewise, the suppression of ASR magnitudes in Occidental low saccharine consuming rats is not recapitulated by substituting corticosterone administration for the shock exposure [36]. Therefore, a role of glucocorticoids in the suppression of ASR magnitudes may be limited.

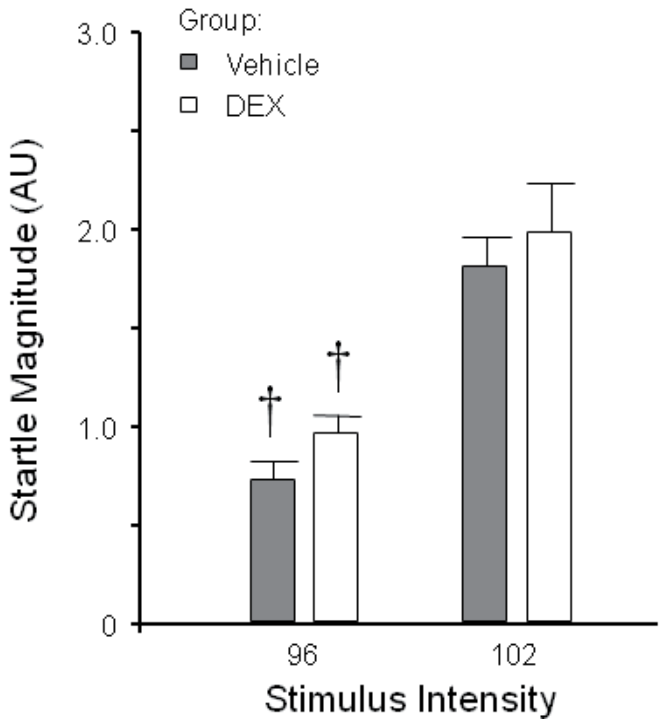

Figure 2. In order to increase binding at the glucocorticoid receptors, the synthetic glucocorticoid analog, dexamethasone, was administered s.c. (0.1 mg/kg) to female Sprague Dawley rats (n= 8-9). The magnitudes of the elicited ASRs only differed across the Stimulus Intensity, $F(1, 15) = 135.3$, $p < .001$, not drug administration. Data are collapsed over the 2 startle test sessions. A cross (†) represents within-group difference from the highest stimulus intensity ($p < .05$, Fishers LSD).

3.2. Pro-inflammatory cytokines

The second mechanism, which is intertwined with the HPA-axis, is the peripheral pro-inflammatory immune response. We first showed that a ovarian hormone-dependent suppression of startle magnitudes could be induced by a single injection of the pro-inflammatory cytokine interleukin (IL)-1β [34], an effect that appears to parallel that observed following tailshock [31]. This effect was later replicated in male rats using lipopolysaccharide (LPS) [35]. Still, peripherally released IL-1β elicits the release of glucocorticoids from the adrenal through stimulation of the vagus nerve, paraventricular nucleus of the hypothalamus, and pituitary gland, which provides an anti-inflammatory response to the pro-inflammatory signal [39-44]. In order to further delineate that pro-inflammatory cytokines, and not anti-inflammatory glucocorticoids, are necessary for stress-induced startle suppression, we compared the effect of inescapable tailshock upon the induction of ASRs in two strains of rats, specifically chosen because of their pro-inflammatory and glucocorticoid responsiveness to stressors. Low-glucocorticoid/high-pro-inflammatory releasing Lewis (LEW) rats [45-49] and high-glucocorticoid releasing Wistar-Kyoto (WKY) rats [50-52] were compared.

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Females of each of these strains were exposed to inescapable tailshock and subsequently tested for startle reactivity 1 and 3 h later. If pro-inflammatory signaling, not anti-inflammatory glucocorticoid release is critical for eliciting startle suppression, then LEW rats would exhibit suppression of the ASR, and the WKY rats would not. As shown in Figure 3, this is the case. This suggest the suppression of startle responsivity in female rats is more likely due to an overactive pro-inflammatory cytokine signaling response, instead of an overactive anti-inflammatory glucocorticoid response via the HPA-axis.

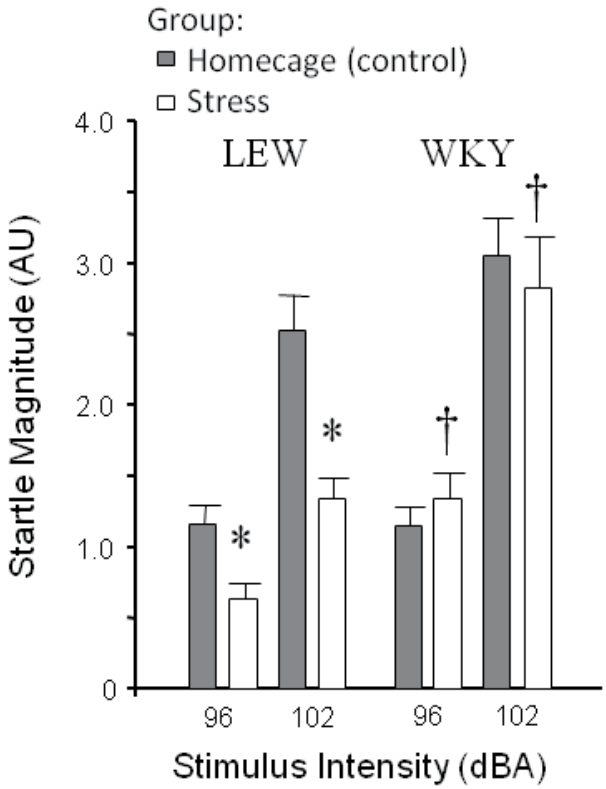

Figure 3. LEW rats exposed to the stressor differed from both their same-strain controls and the WKY groups on the measure of startle magnitude (responsivity). These impressions were confirmed by both main effects of Stimulus Intensity, $F(1, 36) = 285.0$, $p < .0001$, Strain, $F(1, 36) = 6.4$, $p < .02$, and Stressor exposure, $F(1, 36) = 5.3$, $p < .03$, as well as a marginal Strain x Stressor interaction, $F(1, 36) = 3.3$, $p < .07$. In addition to the expected differences in ASR magnitude due to Stimulus Intensity, $F(2, 72) = 186.5$, $p < .0001$, there were differences in the number of elicited startles across the two strains at the lowest stimulus intensity, with WKY rats having responded with more startles (4.5) than did the LEW rats (3.8) to 92 dBA stimulus. This impression was confirmed by a significant Strain x Stimulus Intensity interaction, $F(2, 72) = 3.0$, $p < .05$ (data not shown).

The hypothesis that pro-inflammatory cytokines are a necessary component in the suppression of startle responses following stress was further evaluated in the immune-sensitive Lewis rat strain by determining if elevations of peripheral IL-1β is sufficient to suppress startle reactivity in female rats. Startle responsivity has been found to be suppressed in female SD rats

[34], but, we questioned whether immune-sensitive Lewis rats would show either greater effect sizes in the suppression of the startle magnitudes and/or reduced startle sensitivity as well. As shown in Figure 4, both startle responsivity and sensitivity were reduced in female Lewis rats administered IL-1β. This confirms that pro-inflammatory signaling can influence both aspects of startle behavior, with sensitivity effects requiring a greater sensitivity to the pro-inflammatory signals or, possibly, greater elevations of the signal.

3.3. Prior immune challenge effects on stress-induced startle in SD rats

One consequence of the peripheral immune system having an effect on behavior, in this case sensory reactivity to acoustic stimuli, is that prior immune challenges may influence how future pro-inflammatory signaling or anti-inflammatory glucocorticoid responses influences behavior following stressor exposure. LPS is a commonly used endotoxin that elicits sickness behaviors due to a release of peripheral and central pro-inflammatory cytokines, followed by an increase in circulating glucocorticoids [53, 54]. Others have shown that immune challenges days prior to shock exposure causes a greater increase in glucocorticoid release in response to shocks [55, 56]; therefore, we used this known method of causing a sensitized glucocorticoid response to determine if a greater glucocorticoid release enhances or reduces the degree by which tailshock suppresses startle responsivity.

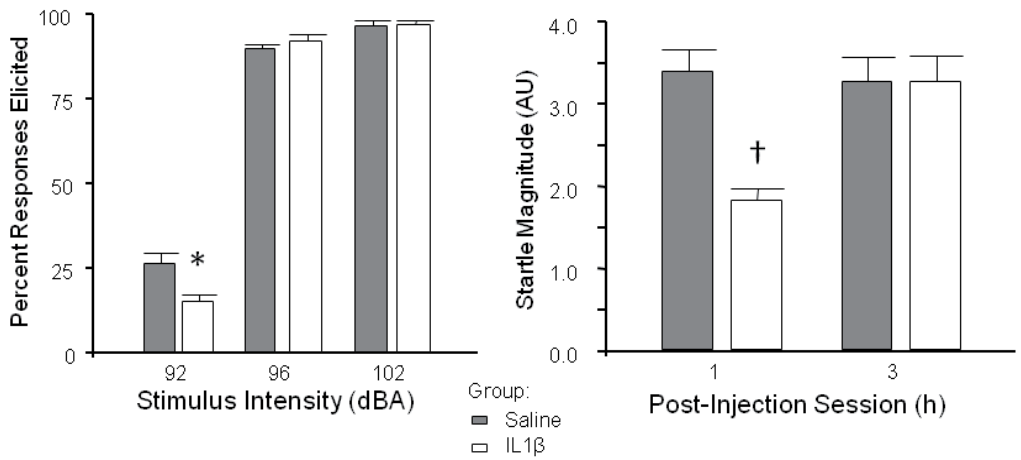

Figure 4. Female LEW rats (n = 16) exhibited significant differences in both startle sensitivity and startle responsivity measures following a single systemic injection of IL-1β (3 μg/kg, i.p.). Startle sensitivity was equally effected 1 and 3 h following administration and is shown collapsed over Session Time. Startle responsivity was only effected 1 h following administration; therefore, the 3 h time-point is not shown. An asterisk (*) represents a significant difference from saline-treated controls at the same stimulus intensity. A cross (†) represents a significant difference from saline-treated controls during the same test session (all $p < .05$, Fishers LSD).

We hypothesized that pro-inflammatory signaling causes stress-induced startle suppression; therefore, experiencing an immune challenge 3 days prior to shock would cause a sensitized anti-inflammatory release of glucocorticoids in response to inescapable shock, blocking the reduction of startle responsivity caused by the acute release of pro-inflammatory cytokines.

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As expected, the number of startle responses elicited did not differ based on prior treatment but did differ across stimulus intensity (data not shown); however, prior exposure to LPS reduced the effectiveness of inescapable shock to attenuate startle magnitudes (see Figure 5). Although LPS has a short-term suppressing effect upon the startle response [35], it both causes an acute increase in pro-inflammatory cytokines (and sickness behaviors) followed by an increase in anti-inflammatory glucocorticoid signaling. This "priming" effect upon the anti-inflammatory glucocorticoid response to shock is a likely mechanism for "buffering" the behavior from being affected. Again, this suggests the glucocorticoid response may actually counteract the suppressive effects originating from peripheral pro-inflammatory cytokine signaling.

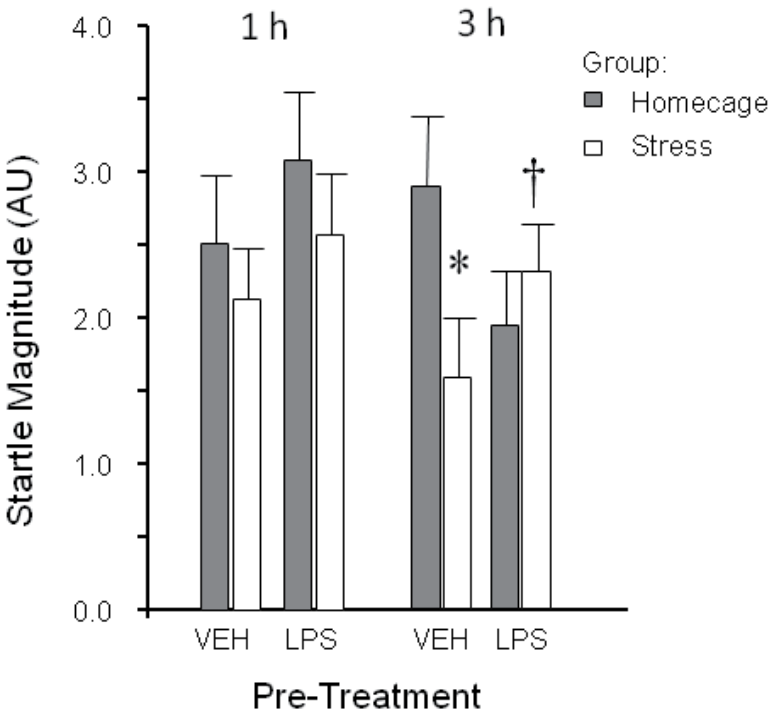

Figure 5. The expression of stress-induced startle suppression became evident 3 h following stressor exposure; however, this effect was blocked in those rats previously exposed to 30 µg/kg LPS (i.p.) 3 days earlier. These impressions were confirmed by a significant LPS x Stress x Session interaction, $F(1, 28) = 10.2$, $p < .005$. Hence, the pretreatment with LPS, which should have increased the glucocorticoid response to the inescapable tailshocks, blocked the suppression of startle responsivity following shock exposure. This suggests that prior experiences likely cause a more robust anti-inflammatory glucocorticoid response that actually *reduces* the influence of the peripheral immune pro-inflammatory immune response upon the areas of the brain capable of suppressing startle responsivity.

4. Central mechanisms of reduced startle reactivity

4.1. Neuroanatomy and endocrine modulation of startle suppression

As mentioned above, studies of pre-pulse inhibition of the ASR have elucidated neural circuitry that underlie the suppression of ASRs when they are immediately preceded by a salient auditory stimulus, for a review see [57]. Both the BNST and AMG have indirect projections to the PnC through the PPT [58]. Inputs from the PPT, LDT, and SNR to the PnC cause inhibition of the startle response [7, 9, 59, 60]. More specifically, it appears the magnocellular portion of the PnC has muscarinic receptors to receive the inhibitory cholinergic signal from PPT and LDT [61] and $GABA_B$ receptors receive the inhibitory signal from the SNR [62]. The question is whether these areas could provide more tonic inhibition of the ASR, outside of the attentional processes associated with PPI. For instance, it is known that lesions to the medial septum and the fimbra-fornix increase startle reactivity because these areas provide tonic inhibition upon the amygdala [63]; thus, removal of inhibition upon the amygdala increases tonic excitatory activity to the PnC (from the amygdala). In contrast, lesions to the noradrenergic cell bodies of the LC reduce startle response magnitudes, as these neurons probably serve a tonic excitation function upon the PnC [64]. Thus, there are circuits within the brain that are situated such that they could provide more tonic changes in the ASR.

Specific to the female startle-suppression model, a central mechanism that caused this change in reactivity should be influenced by the presence/absence of ovarian hormones [31, 32]. Ovarian hormones can have a significant impact on many of the neural structures associated with startle regulation. The cochlear nuclei [65], the nucleus accumbens [66], the hippocampus, [67] and the SNR [57] all exhibit changes in morphology, neurotransmission, and/or receptor expression with the presence of ovarian hormones. Yet, despite all these areas of influence, rodent studies usually do not find any differences in baseline startle reactivity across the estrus cycle or with hormone replacement [68, 69]; however, see [70] for an example of oral-contraceptive usage effecting baseline startle in women. When significant arousal or stress occurs in the rodents, however, the modulatory actions of ovarian hormones on startle become evident. For example, Toufexis and colleagues have shown the magnitude of CRH-enhanced startle is attenuated when progesterone levels are increased [71]. CRH is thought to enhance startle reactivity in the BNST via CRF1-type receptors [72-75]. The result is an increase in excitatory afferents signaling to the PnC [76]. One possibility is that progesterone, or its metabolite allopregnanolone, may decrease the excitatory signaling from the BNST to the PnC by increasing GABA inhibition in this structure [77]. However, in vitro, BNST CRF-1 receptors increase local GABA activity [78]. Thus, it appears that progesterone or allopregnanolone should facilitate the actions of CRH on startle, unless they act through different mechanisms within the BNST or outside of the BNST. On the other hand, progesterone also affects how IL-1β influences sexual receptivity [79], and both glucocorticoid receptor activation [77] and progesterone-induced changes in central neuroadrenergic activity [80] have been suggested to attenuate startle reactivity selectively in female rats. As shown in Figure 6, the administration of progesterone to ovariectomized

rats appears to be necessary for IL-1β to suppress startle magnitudes. Thus, ovarian hormones are not sufficient to cause changes in startle reactivity in female rats. In fact, IL-1β appears to increase startle responsivity following estradiol pretreatment (17β-estradiol), whereas progesterone pretreatment sets the stage for IL-1β to suppress startle responsivity. Therefore, stress-induced startle suppression in female rats appears to necessitate a combination of the two factors, a peripheral pro-inflammatory immune response and the presence of progesterone.

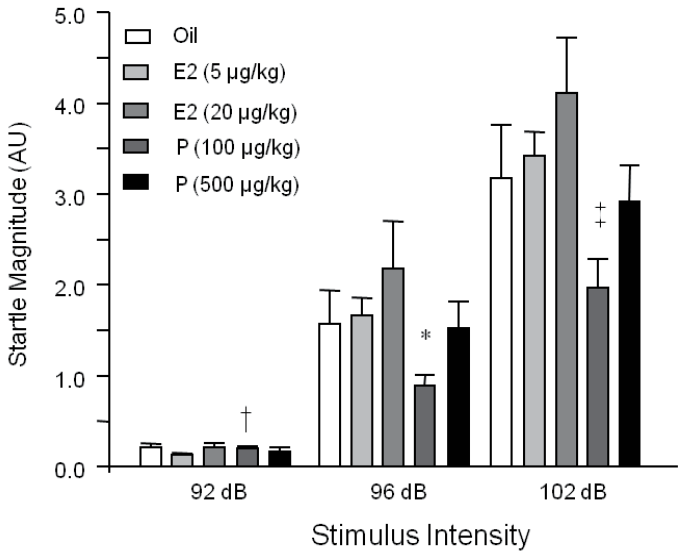

Figure 6. Startle sensitivity and responsiveness were assessed 2 h following IL-1β administration. Hormone treatment occurred 2 h prior to IL-1β injection. Differences in startles elicited (sensitivity) and the magnitudes of those elicited startle responses (responsivity) each were assessed via a 5 (Condition) x 3 (Stimulus Intensity) repeated measures ANOVA. No significant differences in startle sensitivity were detected (data not shown). However, a significant main effect of Stimulus Intensity, $F(2, 70) = 392.2$, $p < .001$ and a significant Condition x Stimulus Intensity interaction, $F[8, 70] = 2.1$, $p < .05$ were detected in the measure of startle responsivity (magnitude). An asterisk (*) represents a significant difference from all other groups. A single cross (†) represents a significant difference from the low estradiol dose group. A double cross (‡) represents a significant difference from both estradiol-treatment groups. All post-hoc tests used Fishers LSD ($p < .05$).

4.2. Evidence for limbic regulation of startle suppression

Peripheral IL-1β is known to have a significant impact on brain activity. Systemic IL-1 administration activates key afferent pathways in brainstem (lateral parabrachial nucleus and dorsomedial and ventrolateral medulla) and limbic system nuclei (BNST and central nucleus of the amygdala) [81]. In fact, peripheral IL-1β activates the amygdala and BNST more than i.c.v. administered IL-1β [82], probably because the vagal-mediated signals to these nuclei are more direct, to those nuclei via the NTS, than the diffusion of the IL-1β from the ventricles. Still, increasing peripheral IL-1β signaling increases NE and serotonin levels in these

brain areas [83] and noradrenergic metabolism in the paraventricular nucleus of the hypothalamus (PVN), locus coeruleus (LC), and amygdala [83]. In fact, as the IL-1β dose is increased, the amount of NE metabolism increases linearly in the amygdala, lasting as much as an hour [83]. It should be noted, this was not tested in the BNST. Yet, stimulation of α-adrenergic receptors also attenuate startle responses and facilitate non-associative habituation of the startle response [84-88]. IL-1β affects activity in the LC in a dose dependent manner as well, with low doses inhibiting activity and higher doses causing excitation; a process mediated by CRH at the time of IL-1β release [89]. Further, when the exposure to painful stimuli is prolonged or LPS is used to cause a significant pro-inflammatory response, additional release of central IL-1β occurs, especially in the hypothalamus [90, 91]. These data suggest that activity in the limbic system, monoamine activity in particular, is significantly affected by peripheral immune signaling.

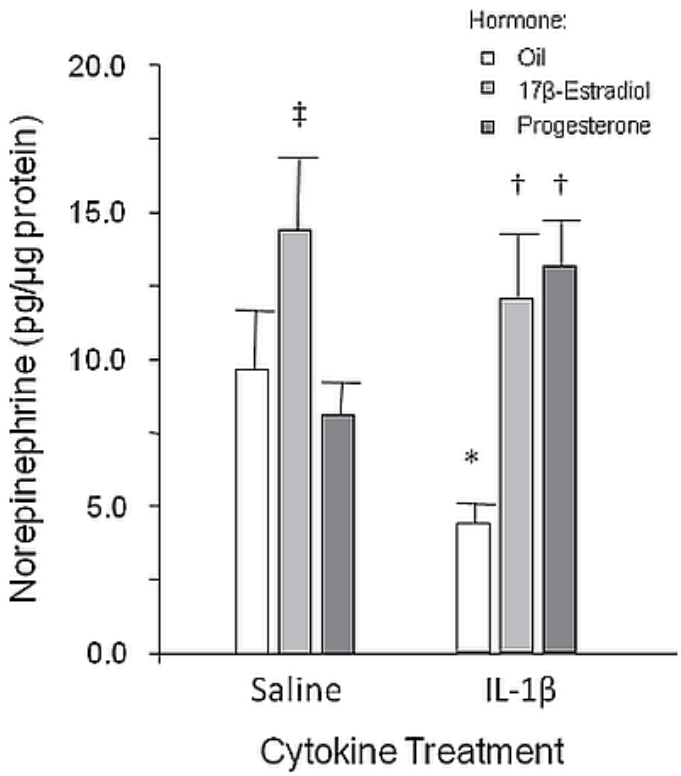

Figure 7. Significant effects of IL-1 treatment on NE levels in the BNST were observed in rats pretreated with progesterone (100 µg/kg, s.c.). This was confirmed by a significant Hormone x IL-1 interaction $F(2, 42) = 4.5$, $p < .02$. IL-1β treatment to oil-treated controls was associated with significantly lower NE levels than oil-treated saline-controls (*). IL-1β-administered rats, which were pretreated with either estradiol [20 µg/kg, s.c.) or progesterone, exhibited higher levels of NE compared to oil-pretreated rats that subsequently received IL-1β (†). In addition, the 2 hormone treated saline control conditions also differed from each other, with the estradiol-treated saline-controls exhibiting higher levels of NE than those pretreated with progesterone prior to saline administration (‡). All post-hoc tests utilized Fisher's LSD ($p < .05$).

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Based on the above logic, we hypothesized that the reduction in ASR magnitude occurring as a result of IL-1β administration to progesterone-pretreated female rats could be associated with changes in the central noradrenergic activity in one of the known modulatory nuclei of the acoustic startle response. Therefore, we measured norepinephrine levels in brain tissue-punches from 4 brain areas: BNST, amygdala, medial prefrontal cortex (mPFC), and dorsal hippocampus. As stated above, both the BNST and cAMG have direct excitatory projections to the PnC and indirect inhibitory connections via the PPT. The medial prefrontal cortex projects to the primary startle circuit via the LDT, whereas the dorsal hippocampus was included as an area that is both reactive to stress and ovarian hormone manipulation, but it is actually several synapses removed from the PPT. As shown in Figure 7, differences due to hormone pretreatment and subsequent IL-1β administration were found in the BNST, not in any of the other 3 areas.

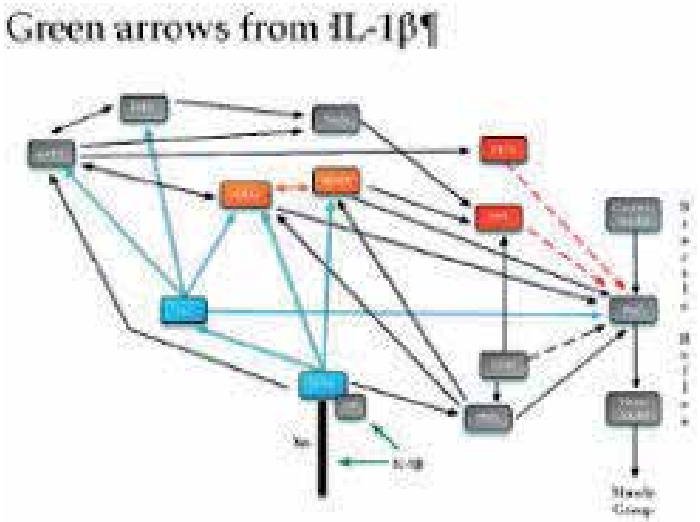

Figure 8. Beyond the direct connections of the brainstem/midbrain nuclei, there are many other nuclei that indirectly influence the modulation of the ASR. Graphically represented here are the noradrenergic projections (in blue) from the nucleus of the solitary tract (NTS) and locus coeruleus (LC) to the various nuclei of the limbic system that then modulate the ASR via the inhibitory brainstem/midbrain nuclei. Input to the NTS via either the from the vagus nerve (X n.) or diffusion of IL-1β across the blood-brain barrier in the nearby area postrema is necessary for the noradrenergic changes in the brain in response to peripheral pro-inflammatory cytokine signaling. As above, red lines denote cholinergic pathways, and dashed lines represent inhibitory circuits. The orange represents CRH-mediated neural circuits. See text for further details.

The role of the BNST in this cytokine-induced change in behavior is logical given recent work associating activity in this structure with changes in behavior associated with behavioral depression or sickness behavior. For example, an endotoxin-induced suppression of social interactions is both associated with increased activity in the BNST as well as reduced activity in the BNST when the suppressed behavior is blocked by IL-1ra [92]. Similarly, the behavioral depression exhibited in the forced-swim test can be reduced by stimulating the vagus nerve, leading to changes in brainstem nuclei activation (including the NTS) and also

activation of the BNST [93]. Others have shown NE release is elevated with stressor exposure in the BNST, which is necessary for some stress-induced behaviors [94, 95]. With particular attention to the startle reflex, the BNST is commonly associated with enhancing startle reactivity [2, 96]. However, as shown in Figure 8), there is an inhibitory pathway from the BNST to the PnC via the PPT that has been examined as a cholinergic mechanism for eliciting PPI [97, 98]. Further, PPI has been shown to fluctuate over the estrus cycle, while not being sensitive to apomorphine disruption, implicating a non-dopaminergic mechanism for these hormone-induced changes in female pre-pulse inhibition, which could rule-out a role of the substantia nigra in this process [68]. In addition, the changes in measured NE levels in the BNST are consistent with previous studies citing peripheral IL-1β administration as a trigger for central noradrenergic activity [82, 99].

There is evidence that could suggest a connection between the known effects of peripheral cytokine activity upon brain noradrenergic activity (most reported males) and an ovarian hormone influence upon these processes. For one, there is growing information pertaining to ovarian hormone influences on noradrenergic activity initiated from the NTS. Many of the brainstem noradrenergic nuclei, including the NTS, exhibit cyclic changes in estrogen and progesterone receptors [100]. Removal of ovarian hormones with or without hormone replacement particularly has a significant impact on NTS physiology. Specifically, the mRNA for prolactin-releasing peptide (PrRP) in noradrenergic neurons is decreased by ovariectomy and increased with subsequent replacement of either estradiol or progesterone [101]. Although the PrRP mRNA levels are reported to not change significantly across the estrus cycle in the NTS, an inspection of the data suggests the levels are a bit higher during proestrus [102]. PrRP labeling in the NTS is also preferentially sensitive to painful stressors, such as tailshock [103]. Estradiol has also been reported to increase neural inhibition in the NTS [104]. These data suggest ovarian hormone influences on NE NTS physiology could occur through changes in the regulation of a co-expressing neuropeptide. This could serve a filtering function for the vagal activity representing immune activity changes in the periphery, as the NTS projects its NE efferent connections to key areas involved in arousal and sensory reactivity, such as the BNST, AMG, hypothalamus, and parabrachial nucleus [105]. For example, core body temperature increases from peripheral IL-1β occur for a longer period of time during proestrus (compared to diestrus) apparently do to the actions of progesterone [106]. Although it is clear hypothalamic cyclooxygenase is the necessary mechanism for this effect [107] the noradrenergic input to the hypothalamus is required and may be changed as well [108]. Therefore, there are anatomical and pharmacological reasons to link NTS noradrenergic projections to the BNST as the primary pathway by which changes in vagal activity could influence startle responsivity through known inhibitory circuitry.

Other possible mechanism for startle suppression could occur as a cascade of effects that begin with the hormone-specific effects upon NE in the brain, but end with non-specific hormonal influences upon 5-HT. NE was shown above to be changed in the BNST following systemic increases in IL-1β, confirming the results of others showing noradrenergic activity increases within 30 minutes of a peripheral injection of IL-1β and may last 2 hours [109, 110]. Importantly, as proposed above, the effect of systemic IL-1β injections on brain NE in rodents is dependent upon transmission in the vagus nerve [111]. The effects of peripheral IL-1β on 5-HT are quite different in terms of timing, route, and influence of ovarian hormones. First the increases observed in brain serotonin metabolism are evident 2-4 h following IL-1β administration and,

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at least in male rats, are reported to be less region specific (compared to NE activity changes) [110]. In addition, the effects of peripheral IL-1β on brain 5-HT are not dependent upon the vagus nerve in male mice but neither are the effects upon brain NE activity [112]. Thus, it is not known if 5-HT requires the same pathway as IL-1β to effect central 5-HT activity, but the difference in the temporal cascade would suggest such a difference is logical. Further, as shown in Figure 9, the same peripheral IL-1β injections that elicited a hormone-dependent change in BNST NE levels caused an increase in 5-HT activity in both estradiol and progesterone-treated female rats. This somewhat conforms to the data previously describing less specificity in the upregulation of 5-HT activity, although we did not observe this pattern beyond the BNST.

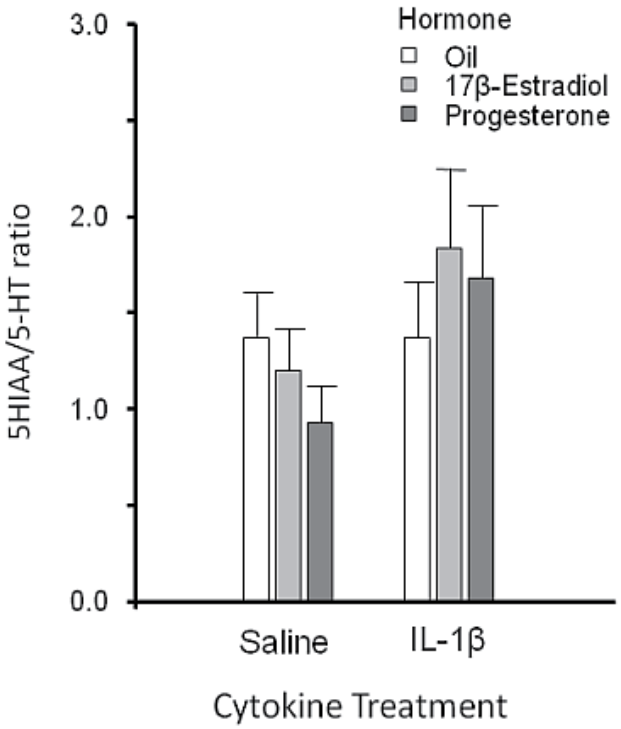

Figure 9. Serotonin activity (5HIAA/5HT ratio) appears to be increased in the BNST of hormone-pretreated OVX female rats 2 h after a systemic injection of IL-1β, as suggested by a marginal effect of IL-1β, $F(1, 42) = 3.6$, $p < .06$.

5. Immune mechanisms following the acute pro-inflammatory response: Recovery or maintenance?

5.1. Recovery of startle responsivity

The peripheral immune system also has counter-inflammation mechanisms that could also be potential mechanisms for what appears to be a pro-inflammatory cytokine-mediated ef-

fect. Thus, another response to pro-inflammatory cytokine release, is the increase in the endogenous IL-1 receptor antagonist (IL-1ra), which has been shown to attenuate the reductions in food-intake elicited by systemic administration of LPS or IL-1β [113]. Our hypothesis was that elevations in IL-1ra, from systemic administration, would counteract the effects of IL-1β. Thus, IL-1ra was administered systemically, followed by an assessment of startle reactivity 1 and 3 h later. As shown in Figure 10, the peripheral immune mechanism for stifling the pro-inflammatory response of IL-1β is sufficient to increase startle sensitivity. This suggests the nervous system is responsive to elevated acute pro-inflammatory signaling, suppressing startle, and elevations in the counter-active IL-1ra, increasing sensitivity to acoustic stimuli. These interactions illustrate the constant inter-relationship between the peripheral immune system and the nervous system regulation of sensory-motor activity.

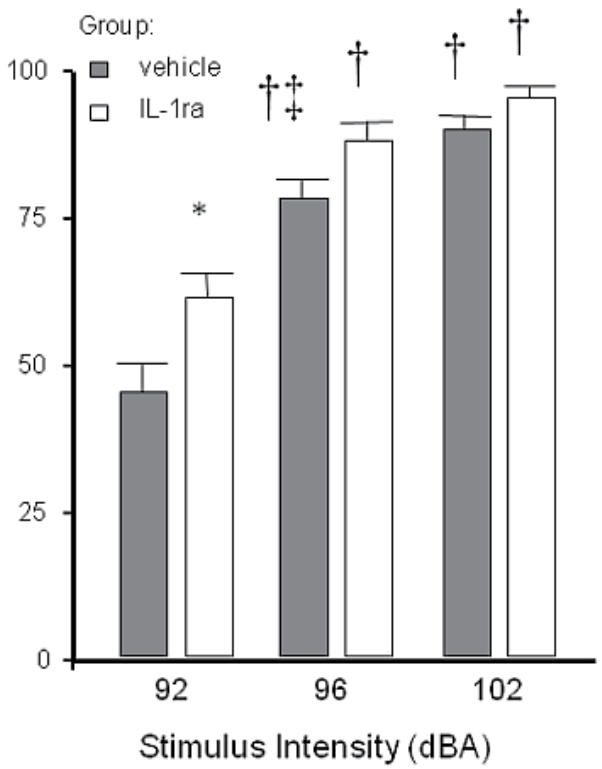

Figure 10. Startle magnitudes in female SD rats (n = 7) were not affected by the administration of IL-1ra (10μg/kg); however, ASRs were elicited more often following the administration of IL-1ra. These impressions were confirmed by a significant main effect of Drug F (1, 12) = 9.7, p <.01. The higher sensitivity to the stimuli was superimposed upon the general difference in elicited startles across the three intensities, as reflected by a main effect of Stimulus Intensity, F (2, 24) = 67.4, p <.0001. An asterisk (*) represents a significant between-group difference from the vehicle-treated controls at the same intensity. A cross (†) represents a significant within-subject difference from the lowest intensity, and a double cross (‡) represents a significant within-subject difference from the highest intensity (all p <.05, Fishers LSD).

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5.2. Immune influences on serotonin synthesis: A possible central mechanism of continued suppression?

Serotonin (5-HT) is an essential modulator of the startle reflex and disruption of serotonin synthesis and metabolism has been shown to result in startle suppression. As shown in Figure 11, during the synthesis of serotonin, L-tryptophan is converted to 5-hydroxytryptophan (5-HTP) by the enzyme tryptophan hydroxylase. In a subsequent reaction, 5-HTP is converted to 5-HT by the enzyme L-aromatic amino acid decarboxylase. Disruption to any part of the 5-HT synthesis pathway is capable of reducing whole brain levels of serotonin resulting in unique abnormalities to the startle reflex. For example, when normal fasted women were tested after having ingested a tryptophan-free amino-acid mixture, the result was lower ASR magnitudes compared to those that received a mixture with L-tryptophan in its contents [114]. When a similar study was conducted in men, a non-significant trend for the same effect appears evident, although it was represented in the analysis as a failure to obtain significant PPI [115]. Alternatively, increasing tryptophan catabolism has also shown to affect PPI. Increasing levels of kynurenine, the first product of tryptophan degradation via indoleamine2, 3-dioxygenase, disrupts PPI in male Sprague-Dawley Rats [116]. Thus, the balance of serotonin and kynurenine is a likely secondary mechanism the body uses to modulate startle sensitivity and responsivity to stimuli.

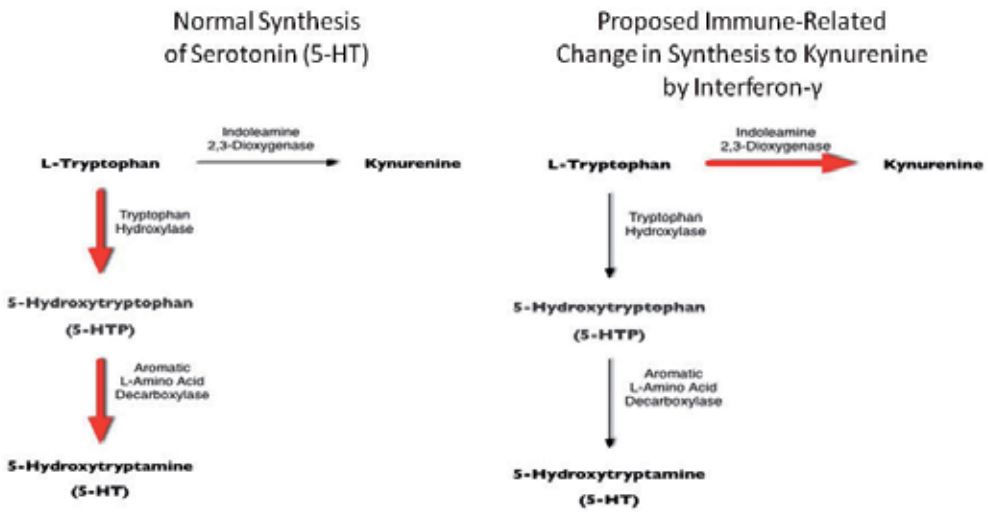

Figure 11. The normal synthesis of serotonin (5-HT) involves the metabolism of tryptophan to 5-hydroxytryophan by tryptophan hydroxylase; however, in the presence of interferon-γ, another, competing enzyme, indolamine1,3-dioxygenase is upregulated. The result of this shift in the metabolism of tryptophan towards the formation of kynurenine is a reduction in the amount available for metabolism towards the formation of serotonin (i.e. serotonin depletion).

In addition to exhibiting reduced startle responses [18] women exhibiting PTSD, linked to previous intimate partner violence, also exhibit greater circulating levels of interferon (INF)-

γ [117]. INF-γ is a downstream Th-1 mediated signal from the pro-inflammatory IL-1β signal and is a potent inhibitor of 5-HT synthesis, decreasing the amount of tryptophan available for 5-HT production. In the presence of IFN-γ, tryptophan is shunted to kynurenic acid synthesis by increasing activity of indoleamine2, 3-dioxygenase [118]. An intermediary signal between IL-1β and INF-γ is IL-2. Female rats treated with IL-1ra (to combat the induction of EAE) exhibit an attenuated IL-2 response [119], which would, presumably, decrease INF-γ signaling (see Figure 12). There is limited experimental evidence that has focused upon delineating INF-γ or IL-2 effects on startle reactivity in rats, and those that have been conducted use an early development administration paradigm to assess later changes on behavior (e.g. [120]). However, one study conducted in mice did access acute IL-2 effects upon startle reactivity and reported no change in behavior [121]. Unfortunately, that study did not test more than one time-point and only utilized male mice.

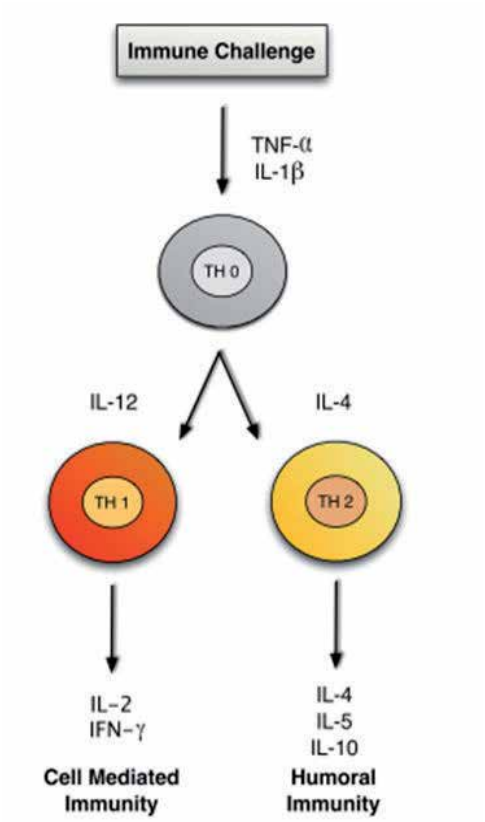

Figure 12. The initiation of an inflammatory response begins with the non-specific macrophage pro-inflammatory response (Th0), which then diverges into either a Th1 (cell-based) or Th2 (humoral-mediated) response. There is evidence that suggests ovarian hormones may influence the path of the subsequent immune cascade from the Th0 response. To date, the Th1 response has been more intently studied for its possible role in effecting behavior (i.e. causing changes in behavior).

Given the lack of data pertaining to IFN-γ effects upon startle sensitivity and responsivity, we conducted a study focusing on determining whether IFN-γ could change ASR sensitivity or responsivity. As stated above, LEW rats exhibit greater pro-inflammatory responses to infection than do other strains; therefore, we tested whether acute administration of IFN-γ is sufficient to reduce startle reactivity, presumably from reducing serotonin availability. Although still preliminary, our results suggest IFN-γ may have a bi-potential effect on startle sensitivity. The higher dose of IFN-γ caused an apparent decrease in the percentage of startles elicited 1.5 h following injection, whereas the lower dose caused significantly more startles to be elicited than the high dose (see Figure 13). This is an important distinction, for it suggests that reduced startle responding due to IFN-γ (and possibly low serotonin tone) is due to a decrease in the ability to sense a startling stimulus, rather than the ability to mount the physical response (although there are trends suggesting that responsivity may be decreased as well with higher doses). Hence, there may be more than a hypothetical link between stress, IL-1 release, and an identified difference in basal immune functioning in a population of women with PTSD that have also been described to have blunted startle responses. There may be instances where the downstream Th1-response is elevated, thus causing a seemingly similar "blunting" of the ASR but the suppression is different in form and occurs through different neural pathways.

6. Clinical applications

The suppression of startle reactions has only gained significant attention in the past decade, and, as researchers have looked for *changes* in startle responses (not just exaggerations), suppression has been observed in anxiety disorders (i.e. PTSD), MDD, and BPD. However, what does it mean when a specific, directional change in a reflex behavior is observed across these different diagnoses? The answer may lie in what is generally called *comorbidity*.

When one considers stress-related mental disorders, typically, anxiety disorders, MDD, BPD, and maybe even schizophrenia are cited as examples, but how distinct are anxiety disorders from MDD or MDD from BPD? In all cases, there is an overlap of various symptoms that could be experienced with any of these diagnoses. The DSM clinical criteria do provide some flexibility in categorizing subjects into the different classes of disorders. What that allows for are physiological conditions that are not specific to just one of these classes, and chronic or phasic abnormalities in the activities of the peripheral immune system could be common in some patients that meet the criteria for PTSD, the non-mania phase of BPD, or even MDD.

For example, there is a growing body of literature that suggests abnormal immune system signaling may be at the core of BPD. Several studies have shown abnormalities in the cytokine profiles of BPD patients, with differences present in both depressed and manic subpopulations [122-124]. Multiple studies have shown a characteristic increase in TNF-α among both bipolar depressed and manic patients [122, 123], whereas patients suffering from bipolar mania commonly exhibit decrease in IL-1β, IL-2, and IFN-γ. When stimulated with LPS,

a common procedure used to model behavioral depression in animals, the monocytes from non-lithium treated patients exhibit a decrease in the production of IL-1β and an increase in IL-6, compared to healthy controls. This abnormality was shown to be reversed in lithium treatment patients [125]. This suggests a by-product of lithium administration may be an influence on the pro-inflammatory response signals in the periphery. Additionally, Boufidou and colleges found that lithium is capable of down regulating the production of IL-2, IL-6, IL-10 and IFN-γ from peripheral blood lymphocytes in BPD patients, and a similar down regulation of pro-inflammatory cytokines was observed in previously non-medicated BDP after three months of lithium treatment [126]. These data further implicate a peripheral immune mechanism for BPD that is normalized by lithium treatment.

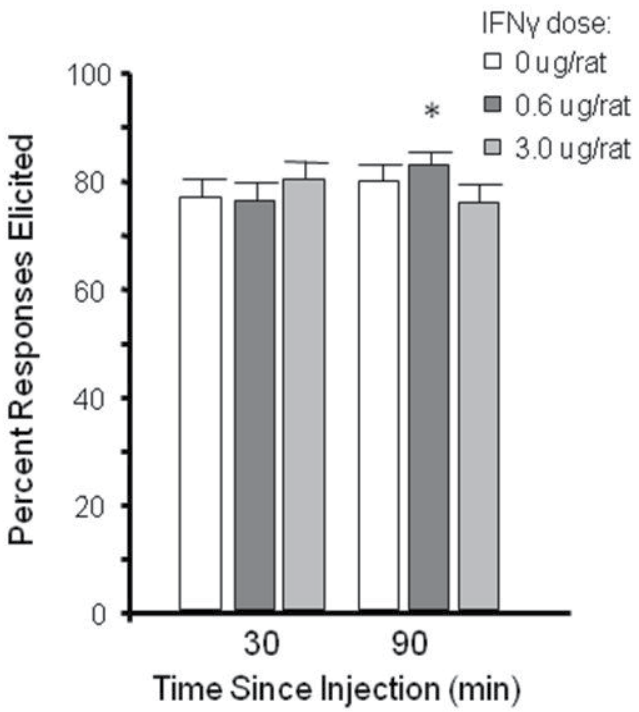

Figure 13. Startle sensitivity and responsivity were assessed 30 and 90 min following an acute systemic injection of IFN-γ (n = 16). Startle sensitivity was significantly altered by the specific dose administered. The low dose showed an increase in elicited startles over time, whereas the high dose showed a reduction in elicited startles over time, IFNγ x Session $F(2, 29) = 3.3$, $p < .05$. An asterisk represents a significant difference in the low-dose group at the 90 min test as compared to the same time high-dose and the 30-min low-dose test.

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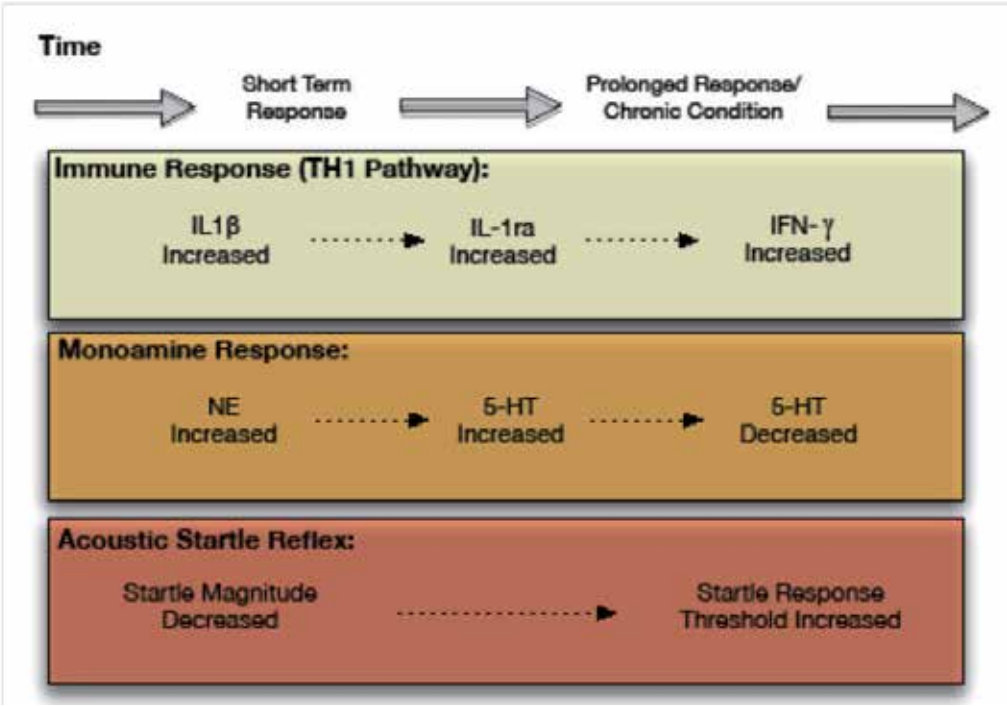

Figure 14. Based on the literature and the collected data from our laboratory, concerning the modulation of the ASR, we propose the following cascade of events may occur as a result of stressor exposure in our female rat model. First, the acute-phase (pro-inflammatory) response causes a transient reduction in startle responsivity (magnitude) that appears to last as long as IL-1 continues to be elevated above the levels of circulating IL-1ra. IL-1ra serves to normalize the response; thus, when the levels of IL-1ra are elevated to a sufficient degree, it causes an increase in ASR sensitivity (a rebound effect). However, in the cases where the stressor exposure is prolonged and/or severe enough to engage a downstream Th-1 response (i.e. increase IFN-γ signaling), then a reduction in ASR sensitivity occurs, whereby the sensory threshold for eliciting the response is increased. This could cause a chronic condition where ASRs are "blunted" in people with conditions ranging from PTSD to MDD to BPD.

The ASR could have a potential use as a functional index of abnormal peripheral immune functioning; thus, if the ASR is suppressed, it may represent an elevated level of pro-inflammatory or Th1 signaling in the patient. This could be of great importance from a therapeutic standpoint when one considers the suppressive effects of IL-1 upon sexual motivation in female rats are attenuated by indomethacin and ibuprofen [127]. Although blocking prostaglandin synthesis [128] or knocking-out the prostaglandin EP2 receptor does not change startle reactivity [129], prostaglandin EP1 knock-out mice do exhibit higher startle magnitudes compared to their wild-type control strain [130]. This suggests that EP1 receptors are in a position to serve as neuroimmune mechanisms to inhibit startle responsivity as well. Still, beyond the possible pharmacological implications, blunted reactivity to stimuli can have profound effects on other neural processes as well, and may explain some of the other symptoms associated with anxiety, MDD, or BPD. For instance, when the same dose of IL-1β, sufficient to blunt startle responsivity in female SD and Lewis rats, is administered to female SD rats prior to a simple associative learning procedure the rate of learning is

slowed. This effect is attributed to a reduction in the neural representation of the unconditional reflexive response (i.e. the response is weaker), causing less optimal neural representation of the behavioral response to the predictive, conditional stimulus [131]. The implication is that associative learning may be impaired by either acute or chronic elevations in pro-inflammatory or Th1 cytokines. Interestingly, this pattern of effect is not observed in male rats, at these low to moderate dosages of IL-1β; in fact, these learning processes are facilitated [132, 133]. Thus, the ASR can serve as a tool to better understand the blunting of sensory reactivity, but may also have implications for more complex associative learning processes as well. In Figure 14, we present our theory as to how the ASR may be changed over time as a function of neuroimmune interactions between peripheral cytokine signaling (specifically the acute pro-inflammatory response and the downstream Th-1 response) and brain monoamines.

7. Conclusions

The evidence accumulated from these experiments favors a pro-inflammatory mechanism, over a HPA-axis glucocorticoid mechanism, as the necessary pathway that ultimately leads to the suppression of startle reactivity following stressor exposure. This finding adds to the ever-growing evidence that peripheral immune signaling has a significant role in influencing how the nervous systems functions. In this particular case, we have illustrated how a simple behavioral reflex can be dampened by pro-inflammatory signals, in the absence of any physical injury. This shows abnormal levels of peripheral immune signaling could lead to perceived symptoms reported by patients with PTSD, MDD, or BPD.

Biological differences in how different animals respond to stressor may reflect vulnerability factors for experiencing different symptoms associated with stress-related disorders, such as PTSD, MDD, and BPD. Thus, differences observed in the literature concerning startle reactivity in female PTSD patients (e.g. [18, 19]) could be due to the types of stressor exposure or individual differences in biological responses. In addition, one cannot rule-out the role of coping mechanisms. In fact, one could hypothesize that the suppression of startle is an evolutionary selected response that keeps individuals within a species from continuing to fight a "losing battle". If this were the case, then it would be logical for the immune system to play a role in that trigger-mechanism and not the HPA-axis. The HPA-axis is designed to maintain the fight-or-flight response [134], which would be in opposition to a behavioral suppression coping response. Others have proposed females are particularly selected to engage in alternative coping strategies that are in opposition to the fight-or-flight response [135], and one possibility is that signal reception of the peripheral immune response by the central nervous system is an early point of diversion in stress coping strategies between males and females. This could provide inherent propensities to respond differently, but, at the same time, could be modified by experience. Such propensities could translate into vulnerability factors for abnormal behaviors where that response becomes, potentially, maladaptive.

It is well documented that more women experience anxiety disorders and affective disorders, and there is a significant degree of comorbidity across these disorders – especially as cases become more severe [136]. There are many potential reasons for the higher rates re-

ported in women. For instance, some have recently suggested there is a link between ovarian hormones and the occurrence of specific peptide isoforms that modulate stress responsiveness and fear conditioning [137]. The data presented here provide another example of how ovarian hormones can influence physiological processes associated with stress responsiveness. The role of progesterone in this immune model of startle suppression is particularly intriguing since progesterone can amplify the pro-inflammatory response through macrophage migration inhibitory factor [138]. This endocrine influence could, potentially, cause more Th1 signaling to occur, which, we hypothesize leads to an increase in IL-1β, causing more Th1 signaling to occur, eventually leading to an increase in IFN-γ release and subsequent reductions in sensitivity to auditory stimuli. If that same individual has central nervous system vulnerabilities, such as a particular peptide isoform, then, in addition to an apparent blunted startle response, the patient may also be exhibiting flashbacks due to enhanced neural processing of fear-associated memory. Thus, female vulnerability for anxiety and depression symptoms can be seen as a product of multiple mechanisms that modulate the female physiology and behavior in a manner that, at times, may even be counter to fight-or-flight, but, nonetheless lead to changes in nervous system functioning, causing the expression of a particular set of behavioral symptoms.

There is a growing literature pointing towards a complex interaction between the central nervous system and the peripheral immune system that underlies anxiety or affective disorder vulnerability and/or the presence of acute symptoms [139-143]. The utility of being able to use species-common measures, such as the startle response, has been advantageous to researchers in aiding them to understand how the brain functions under normal and abnormal conditions. Here we illustrate how such measures can be applied to the understanding of psychoneuroimmune interaction as they pertain to the influence of the peripheral immune system upon the brain and behavior. As we gain a greater understanding of the signaling cascades in the peripheral immune system, delineating how those signals affect the brain will continue to be important for our future understanding of the etiology of mental illnesses.

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Section 3

Clinical Issues: Old Problems New Ideas

Chapter 7

Social Anxiety Disorder in Psychosis: A Critical Review

Maria Michail

Additional information is available at the end of the chapter

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1. Introduction

Eugene Bleuler was one of the first to emphasize the importance of affect and its pronounced impact upon the course and outcome of psychosis. The famous "*Krapelian dichtocomy*" which supported the clear distinction between mood and psychotic illnesses on the basis of etiological origins, symptomatology, course and outcome was first challenged by Bleuler. Bleuler recognized the disorders of affect as one of the four primary symptoms (blunted *'Affect'*, loosening of *'Associations'*, *'Ambivalence'*, and *'Autism'*) of schizophrenia, as opposed to delusions and hallucinations which were perceived as secondary. Bleuler further postulated the incongruity between emotions and thought content in people with schizophrenia as well as their diminished or complete lack of emotional responsiveness. Bleuler's recognition of the importance of affective disturbances in schizophrenia has influenced current diagnostic definitions and criteria of schizophrenia.

The sharp distinction between affect and psychosis which has dominated both research and clinical practice during the nineteenth and twentieth century has gradually been abandoned. New evidence from epidemiological, familial and molecular genetic studies (Cardno et al, 2005; Craddock et al, 2005; Craddock & Owen, 2005) have come to light demonstrating the endemic nature of affective disturbances in psychosis. In a twin study by Cardno et al (2002), the authors identified significant overlap in risk factors between the schizophrenic, schizoaffective and manic syndromes. Specifically, considerable genetic correlations were reported between the schizophrenic and manic syndromes. This is in accordance with a review of genetic linkage studies of schizophrenia and affective disorders (Wildenauer et al, 1999) which supports the genetic overlap of the two syndromes. Furthermore, factor analytic studies of psychosis symptoms consistently point to a depression dimension in non-affective psychosis (Murray et al, 2005). Depression and social anxiety are each observed throughout the course (Koreen et al, 1993), including the prodromal phase (Hafner et al, 1999; Owens et al, 2005) and following symptomatic recovery. Post psychotic depression

(PPD) has been reported in 30-50% of individuals (McGlashan et al, 1976; Birchwood et al, 2000a) and social anxiety disorder (SaD) has been observed in up to one in three (Davidson et al, 1993; Cassano et al, 1999; Goodwin et al, 2003; Pallanti et al, 2004).

2. Social anxiety disorder

2.1. Definition

According to the DSM-IV (APA, 1994), social anxiety disorder (social phobia) is defined as "a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing". People with social anxiety desire to make a favourable impression during social encounters but at the same time doubt their ability to do so; they fear that they will be scrutinized and negatively evaluated due to perceived failed social performance. These fears lead people with social anxiety to avoid all or some social situations and in extreme cases this could lead to complete social isolation (Clark & Wells, 2005). Exposure to the feared situation is almost always accompanied by physical symptoms, for example, sweating, trembling, heart racing, which could develop (although not necessarily) to panic attacks.

Evidence regarding the distinction of social phobia into two subtypes, the non-generalized and generalized social phobia, is ambiguous; although the DSM-IV does acknowledge the presence of the latter. This encompasses a wider range of fears linked to interaction situations and therefore is not restricted to particular environmental circumstances (i.e. it is "free-floating"). It may include talking to others, asking questions, meeting new people, manifest in fear and avoidance of everyday situations (Wittchen et al, 1999). These kinds of social fears have been exclusively reported in approximately two-third of people with lifetime social phobia indicating that the generalized subtype might be more prevalent compared to the non-generalized one (Kessler et al, 1998). This, sometimes also called "specific" or "discrete", is mainly characterized by performance-type fears, the most common being that of speaking in public or performing in front of an audience (Schneier et al, 1992; Stein et al, 1996). It seems therefore that the generalized subtype reflects a more pervasive and debilitating form of the illness which is supported by evidence showing higher rates of comorbidity with mood and other anxiety disorders (Wittchen et al, 1999) and lower recovery rates, compared to the non-generalized, specific subtype (Kessler et al, 1998).

2.2. Epidemiology and course

One of the largest epidemiological investigations carried out in the United States, the National Comorbidity Survey (Kessler et al, 1994), has reported prevalence estimates of 12-month and lifetime social anxiety disorder as 7.1% and 12.1%, respectively. The lifetime prevalence of social anxiety in other western countries seems to range between 3.1% to 15.6 % (Favarelli et al, 2000; Furmark et al, 1999). The variation in prevalence rates among differ-

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ent epidemiological studies could be attributed to the application of different diagnostic criteria and instruments for the identification and assessment of social anxiety disorder.

Studies investigating the course of social anxiety have established the long-term morbidity of the illness (Chartiers et al, 1998; Yonkers et al, 2001). Social anxiety develops at an early age, usually during childhood or adolescence and once established, follows a stable, chronic course if treatment is not initiated (Chartiers et al, 1998; Yonkers et al, 2001). Recent findings show that social anxiety is also very prevalent in later life (Cairney et al, 2007). Findings regarding the sociodemographic characteristics of social anxiety disorder support that this is more prominent among the female population (Wittchen et al, 1999; Schneier et al, 1992; Davidson et al, 1993; Magee et al, 1996) although there have been studies (Stein et al, 2000) which have failed to confirm such gender differences. Moreover, higher incident rates have been consistently observed among unmarried individuals usually coming from a lower socioeconomic background, with poorer educational attainment and higher unemployment rates (Schneier et al, 1992; Davidson et al, 1993; Magee et al, 1996). The average duration of illness is approximately 29 years (Chartier et al, 1991; Keller et al, 2003) and the likelihood of a full remission or recovery is significantly lower compared to that of other anxiety disorder (Keller et al, 2003). In an eight year longitudinal study of 163 patients with social phobia, Yonkers et al (2001) found that only 38% and 32% of female and men respectively experienced a complete remission indicating the unremitting and persisting nature of the disorder. Additionally, such lower rates of recovery were found to be associated, particularly in women, with a history of suicide attempts, the presence of co-morbid disorders, the most prominent that of agoraphobia, avoidant personality disorder and alcohol abuse, and also with poor baseline functioning (Yonkers et al, 2001; Keller et al, 2003).

The highly impairing nature of the disorder is reflected in the marked disabilities affecting the majority of life domains. Deterioration of social functioning manifest in avoidance and withdrawal from social interactions, decrease in work productivity and interpersonal relations produce a significant decrease in quality of life (Wittchen et al, 2000). Despite the highly impairing nature of social anxiety only up to a half of patients seek and receive treatment during the course of the illness (Wittchen et al, 2000; Wang et al, 2005) and this is primarily in the form of pharmacological interventions.

3. Social anxiety in psychosis

Social anxiety is among the most prevalent and debilitating affective disturbances manifest in people with psychosis (Pallanti et al, 2004; Mazeh et al, 2009; Michail & Birchwood, 2009). In a recent study by Michail & Birchwood (2009), social anxiety was diagnosed in 25% of people with first-episode psychosis (FEP). In addition to the 25% with an ICD-10 diagnosis of SaD, there was also a further 11.6 % who reported clear social interaction difficulties and/or signs of avoidance not sufficient though to reach formal diagnostic criteria. Social anxiety is usually accompanied by high levels of depression (Michail & Birchwood, 2009; Birchwood et al, 2007) and leads to significant social disability (Voges & Addington, 2005), lower quality of life (Pallanti et al, 2004) and poorer prognosis as it raises the possibility of an early relapse (Gumley, 2007).

Despite the high prevalence and its debilitating nature, social anxiety has not been extensively investigated and the processes that underlie its emergence in psychosis remain unclear. The relationship between social anxiety and positive psychotic symptoms, particularly paranoia, is yet to be clarified. Particularly, it is not clear whether the development and maintenance of social anxiety in psychosis is simply driven by paranoia and persecutory beliefs.

4. Aim

This review aims to examine the prevalence and phenomenology of social anxiety disorder in psychosis and to investigate its relationship to positive psychotic symptoms and particularly paranoia and persecutory ideation.

5. Methods

A systematic search strategy was conducted and consisted of electronic searches of the following databases: PsycINFO, PubMed and Science Direct using the terms "anxiety AND psychosis", "anxiety AND schizophrenia", "social anxiety AND psychosis", "social anxiety AND schizophrenia", "social anxiety AND paranoia". For inclusion, studies had to meet the following criteria:

1. Published in an English language, peer-reviewed journal. This ensures a degree of quality assurance in the reviewing process
2. Published between 1990-2011
3. Participants with psychosis. This includes schizophrenia, schizoaffective disorder, schizophreniform, bipolar disorder and depression with psychotic features
4. Adult participants (≥16 years)
5. Diagnosis of social anxiety disorder (either ICD-10 or DSM-IV)

Following the electronic search, hand searches of identified literature were conducted in the form of citation chasing.

6. Results

Thirteen studies fulfilled the inclusion criteria of this review (Table 1): three studies (Cossof & Hafner, 1998; Tibbo et al, 2003; Braga et al, 2005) investigated the prevalence of anxiety disorders, (including social anxiety) in psychosis; six examined the prevalence of social anxiety disorder in psychosis (Penn et al, 1994; Pallanti et al, 2004; Voges & Addington, 2005; Birchwood et al, 2007; Mazeh et al, 2009; Michail & Birchwood et al, 2009), three studies (Lysaker & Ham-

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mersley, 2006; Lysaker & Salyers; 2007; Romm et al, 2012) investigated the relationship of social anxiety with clinical psychotic symptoms and one review paper on anxiety disorders in schizophrenia was also identified (Muller et al, 2004). Four studies recruited a first-episode psychosis sample (Voges & Addington, 2005; Birchwood et al, 2007; Michail & Birchwood, 2009; Romm et al, 2012); three recruited in-patients with schizophrenia, schizoaffective or bipolar disorder (Cossof & Hafner, 1998; Penn et al, 1994; Mazeh et al, 2009) and three recruited outpatients with schizophrenia (Tibbo et al, 2003; Braga et al, 2005; Pallanti et al, 2004).

6.1. Prevalence and phenomenology

Social anxiety appears to be among the most prevalent anxiety disorders in psychosis with prevalence rates ranging between 17% to 36%. In samples with first-episode psychosis, prevalence rates range between 25%-32% based on formal diagnostic criteria (DSM-IV or ICD-10). In a recent study by Michail & Birchwood (2009), social anxiety was diagnosed in 25% of people with first-episode psychosis. However, in addition to the 25% with formal SaD, there was also a further 11.6 % who reported clear social interaction difficulties and/or signs of avoidance not sufficient though to reach formal diagnostic criteria (ICD-10). These "*borderline*" cases, though not satisfying formal criteria, were nevertheless reporting interpersonal difficulties that may well warrant intervention at a clinical level. In studies with inpatient samples, the prevalence of social anxiety ranged between 11%-43% among those with schizophrenia, schizoaffective or bipolar disorder and in studies with outpatients with schizophrenia 17%-36% of them were diagnosed with social anxiety disorder or social phobia.

The highly impairing nature of social anxiety in psychosis has been consistently reported in literature. In a study of outpatients with schizophrenia, Pallanti et al (2004) reported that those diagnosed with comorbid social anxiety disorder had a higher rate of suicide attempts, lower social adjustment and overall quality of life compared to those without social anxiety. Braga et al (2005) also reported higher levels of global functional impairment and greater limitations in the domains of work and social life in schizophrenic patients with comorbid anxiety disorder compared to those without comorbid anxiety disorder. Previous findings by Penn et al (1994) confirm the significant impact of social anxiety on social disability. Findings also show that those with schizophrenia and comorbid social anxiety have higher levels of substance abuse compared to those with no comorbid social anxiety (Pallanti et al, 2004).

The phenomenology of social anxiety in psychosis has been thoroughly investigated by Michail & Birchwood (2009). In their study comparing the severity and phenomenology of social anxiety in psychosis with that in non psychosis, the authors revealed a very similar clinical profile with regards to levels of social anxiety and social avoidance; the number and severity of autonomic anxiety symptoms and social evaluative concerns. What is more, social anxiety both in people with psychosis and non psychosis occurred in the context of an equally high level of other anxiety disorders underlying the similarity of the two groups. The presence of social anxiety in people with psychosis was also accompanied by marked levels of depression; approximately 31% of FEP people exhibited moderate to severe levels of post-psychotic depression. This is in line with findings from previous studies (Voges & Addington, 2005; Birchwood et al, 2007) and confirmed by Romm et al (2012) who found that high levels of social anxiety in people with first-episode psychosis were accompanied by high levels of depression.

Study	Participants	Aim	Key results
Penn et al. (1994)	38 in-patients with a diagnosis of schizophrenia or schizoaffective disorder according to the SCID-P	Investigate the relationship between social anxiety and positive and negative symptoms in schizophrenia	Behavioural indices of social anxiety (e.g. slower speech rated, less fluent speech, global social anxiety) were associated with negative symptoms. Self-report measures of social anxiety and related fears (e.g. fear of being negatively evaluated, fear of walking alone in the streets, fear of talking to people in authority) were associated with positive symptomatology. Such fears may be related to certain aspects of the illness e.g. paranoia, persecutory ideation whereas behavioural manifestations of social anxiety may reflect a deficit in social skills prominent in negative symptom
Cossof & Hafner (1998)	100 consecutive in-patients diagnosed with schizophrenia, schizoaffective disorder or bipolar disorder(based on the SCID)	Determine the prevalence of anxiety disorders in treated psychiatric inpatients with a DSM-IV diagnosis of schizophrenia, schizoaffective or bipolar disorder	43% of inpatients with schizophrenia were also diagnosed with a comorbid anxiety disorder (based on the SCID): 17% social phobia (SP), 12% generalized anxiety disorder (GAD), 13% obsessive-compulsive disorder (OCD)
Tibbo et al (2003)	30 outpatients with a diagnosis of DSM-IV schizophrenia (based on the *MINI*)	Determine the prevalence of anxiety disorders (as assessed by the *MINI*) controlling for anxiety symptoms related to delusions and hallucinations	16.7% prevalence of GAD 13.3% prevalence of SP 3.3% prevalence of panic disorder with/without agoraphobia 16.7% prevalence of agoraphobia without panic, excluding individuals whose anxiety symptoms were related to delusions or hallucinations
Muller et al (2004)	A review of the literature on comorbid anxiety disorders in schizophrenia	Review the epidemiology, phenomenology, and neurobiologic underpinnings of comorbid anxiety symptoms and disorders in schizophrenia, and address treatment strategies	Anxiety disorders are very prevalent in schizophrenia. The mechanisms that underpin this comorbidity require further investigation. Randomized controlled trials of pharmacotherapy and psychotherapy are necessary to establish the best way of managing this comorbidity
Pallanti et al (2004)	80 outpatients with schizophrenia (based on the SCID for DSM-IV) and 27 outpatients with primary diagnosis of social anxiety disorder	Prevalence and severity of social anxiety in schizophrenia Compare the severity and phenomenology of social anxiety in those with schizophrenia and those with social anxiety as primary diagnosis (no schizophrenia)	36.3% of people with schizophrenia were diagnosed with social anxiety based on the Liebowitz Social Anxiety Scale (LSES). The severity of social anxiety and avoidance in this group was as elevated in those with social anxiety without schizophrenia People with social anxiety and schizophrenia had a higher rate of suicide attempts, lower social adjustment and overall quality of life compared to those with schizophrenia only No differences in positive and negative symptoms (as assessed by the SAPS and SANS) between patients with schizophrenia and social anxiety and those with schizophrenia only

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Study	Participants	Aim	Key results
Voges & Addington (2005)	60 patients with first-episode psychosis (FEP)	Examine the relationship between social anxiety and social functioning and determine whether those with psychosis have any maladaptive or irrational beliefs regarding social situations	32% of patients with FEP were diagnosed with social anxiety disorder (SCID-I for DSM-IV) Higher levels of social anxiety, as assessed by the Social Phobia and Anxiety Inventory (SPAI) were related to depression and negative symptoms but not positive symptoms. Social anxiety was associated with greater negative self-statements, and the lack of social anxiety with higher levels of positive self-statements. The authors suggest that negative self-statements may be prominent in the development and maintenance of social anxiety in first-episode patients
Braga et al (2005)	53 outpatients with a DSM-IV diagnosis of schizophrenia	Describe the prevalence of comorbid lifetime anxiety disorders in outpatients with schizophrenia and to compare the subjective quality of life of patients with and without comorbid anxiety disorders	Prevalences of anxiety comorbidity (based on SCID-IV) were: social phobia (17%), OCD (15.1%), GAD (9.4%), anxiety disorder Not Otherwise Specified (7.5%), panic disorder (5.7%), specific phobia (5.7%), Post-traumatic stress disorder (PTSD) (3.8%), and agoraphobia (1.9%) Higher levels of global functional impairment, more severe limitations in the domains of work and social life in schizophrenic patients with comorbid anxiety disorder compared to those without comorbid anxiety disorder
Birchwood et al (2007)	79 participants with first-episode psychosis	1. Examine the rate and severity of social anxiety in FEP 2. investigate the relationship of social anxiety with positive and negative symptoms 3. investigate the relationship between social anxiety and shame of psychosis	29% prevalence of social anxiety in FEP (based on the SIAS/SPS) No relationship between delusions, hallucinations and suspiciousness/ persecution and social anxiety (based on the positive scale of PANSS). Also, no relationship between negative symptoms and social anxiety and avoidance Greater levels of shame attached to their diagnosis and feelings of being down-ranked and rejected in the socially anxious psychotic group compared to the non socially anxious psychotic group
Mazeh et al (2009)	117 inpatients with a SCID-P for DSM-IV diagnosis of schizophrenia	Investigate the prevalence and correlates of social phobia in patients with schizophrenia	11% were diagnosed with comorbid social phobia (based on the SCID-P) Schizophrenic patients with comorbid social phobia had higher (although not statistically significant) level of PANSS total score compare to those without social phobia The "fear" component of social phobia (as measured by the Leibowitz Social Anxiety Scale, LSAS) was related to positive psychotic symptoms Avoidance (as measured by LSAS) was associated with negative symptoms

Study	Participants	Aim	Key results
Michail & Birchwood (2009)	80 participants with FEP	Determine the phenomenology of psychotic SaD and how this is different to non-psychotic SaD Investigate whether psychotic SaD is linked to the nature and severity of psychotic symptoms and particularly paranoia	25% of FEPs received an ICD-10 diagnosis of social anxiety based on the SCAN (WHO, 1999). Equally elevated levels of social anxiety (SIAS), avoidance (SPS), depression (CDSS) and autonomic anxiety symptoms in the psychotic and non psychotic socially anxious group No relationship between positive symptoms including suspiciousness/persecution (PANSS) and social anxiety (SIAS/SPS) in the FEP group. However, a subgroup of socially anxious psychotic people reported higher levels of persecutory threat (Details of Threat Questionnaire) compared to psychotic people without social anxiety.
Romm et al (2012)	144 participants with FEP (based on SCID-I for DSM-IV)	Investigate whether SaD in psychosis is associated with poorer premorbid functioning, higher levels of psychotic symptoms and reduced QoL	50% of FEPs suffered from severe social anxiety (LSAS). Social anxiety was associated with greater levels of depression, poorer premorbid functioning and reduced QoL. No relationship between social anxiety and positive psychotic symptoms was reported.
Lysaker & Salyers (2007)	128 participants with schizophrenia & schizoaffective disorder (based on SCID for DSM-IV)	Investigate the relationship between anxiety (as measured by the Multidimensional Anxiety Questionnaire) and psychotic symptoms (as measured by the PANSS)	Higher levels of anxiety were associated with greater hallucinations, withdrawal, depression, hopelessness, better insight and poorer function.
Lysaker & Hammersley (2006)	71 participants with schizophrenia & schizoaffective disroder	Examine the possible roots of social anxiety in schizophrenia by investigating its relationship to delusions and flexibility of abstract thought	Participants classified as having both significant delusions (based on the PANSS) and impairments in flexibility of abstract thought had significantly higher levels of social anxiety (based on the LSAS) compared to those with only one or neither of these difficulties

Table 1. Studies investigating social anxiety in people with psychosis

6.2. The relationship between social anxiety and positive psychotic symptoms

The relationship between social anxiety and positive psychotic symptoms, particularly paranoia, has attracted considerable attention; however, the processes that underlie this relationship are yet to be clarified. Ten studies identified in this review examined the relationship of social anxiety with positive symptoms (Penn et al, 1994; Tibbo et al, 2003; Pallanti et al, 2004; Voges & Addington, 2005; Birchwood et al, 2007; Mazeh et al, 2009; Michail & Birchwood, 2009; Lysaker & Hammersley, 2006; Lysaker & Salyers, 2007; Romm et al, 2012). Four studies (Penn et al, 1994; Mazeh et al, 2009; Lysaker & Hammersley, 2006; Lysaker & Salyers, 2007) reported a link between social anxiety and positive symptoms. Penn et al (1994) showed that self-report measures of social anxiety and related fears (e.g. fear of being negatively evaluated, fear of walking alone in the streets, fear of talking to people in authority) were associated with positive symptomatology. The authors suggested that such fears may be related to cer-

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tain aspects of the illness e.g. paranoia, persecutory ideation whereas behavioural manifestations of social anxiety (e.g. slower speech rated, less fluent speech, global social anxiety) may reflect a deficit in social skills prominent in negative symptoms. This was also supported by Mazeh et al (2009) who found the "fear" component of social phobia in schizophrenic patients (as measured by the Leibowitz Social Anxiety Scale, LSAS) to be related to positive psychotic symptoms. Lysaker & Hammersley (2006) and Lysaker & Salyers (2007) found that in people with schizophrenia severe social anxiety was accompanied by severe levels of delusions and greater levels of hallucinations, respectively.

Five studies (Pallanti et al, 2004; Voges & Addington, 2005; Birchwood et al, 2007; Michail & Birchwood, 2009, Romm et al, 2012) reported no differences in severity levels of positive symptoms (including paranoia) between those with schizophrenia and comorbid SaD vs no SaD, suggesting that SaD may be unrelated to clinical psychotic symptoms. In a study of young people with first-episode psychosis, Michail & Birchwood (2009) conducted a thorough investigation of the relationship between positive symptoms and social anxiety. The authors compared levels of positive symptoms, including suspiciousness and persecution, as measured by the PANSS (Positive and Negative Symptom Scale) between people with psychosis and social anxiety (FEP/SaD) and those with psychosis only (FEP/no SaD). Findings revealed no differences in PANSS positive symptoms between psychotic individuals with vs. without social anxiety; including no relationship between PANSS suspiciousness/ persecution and social anxiety in the whole FEP (with and without SaD) sample. Furthermore, the level of PANSS suspiciousness/persecution did not affect the severity of social anxiety within the FEP/SaD group itself. These findings confirm previous studies reporting no link between positive symptoms (similarly assessed using the PANSS) and social anxiety (Pallanti et al, 2004; Voges & Addington, 2005) which suggests that the presence of social anxiety in psychosis is not simply driven by clinical paranoia and persecutory threat. It is important to mention though findings in the Michail & Birchwood (2009) study also revealed a subgroup of socially anxious psychotic people (45%) which reported significantly more persecutory threat and anticipated harm as measured by the Details of Threat Questionnaire (Freeman et al, 2001) compared to psychotic people without social anxiety. When investigating further the inter-relationship between social anxiety and persecutory threat within this sub-group no link between level of social anxiety and persecutory threat was revealed. This is of particular interest as it suggests that even among those individuals with psychosis and social anxiety, social anxiety is not necessarily contaminated by ongoing persecutory beliefs.

7. Discussion

Social anxiety is among the most commonly reported and disabling of the co-morbidities in people with psychosis. It is characterized by a highly impairing nature which is evident by its impact on social functioning and social disability. Despite its elevated prevalence and severity in psychosis, social anxiety remains under-recognized and under-treated. One of the reasons for this could be that the exact relationship between social anxiety and psychotic

symptoms is yet to be determined and the available empirical findings are inconclusive. Although theoretical models and empirical evidence consistently point towards a link between general anxiety and positive symptoms of psychosis, predominantly paranoia and persecutory delusions (Freeman et al, 2001), social anxiety appears to have a distinct quality and its relationship to paranoia and persecutory thinking is not straightforward.

Three pathways have been proposed for the understanding of the ontogeny of social anxiety in psychosis (Michail & Birchwood, 2009; 2011) and they are summarized here:

a. social anxiety predates the onset of paranoia and helps maintain persecutory beliefs

This suggests that symptoms of social anxiety, avoidance and withdrawal develop in the early or prodrome phase. This is confirmed by studies showing how social withdrawal and socio-emotional dysfunction in people identified as being at risk for developing psychosis are highly predictive predicting of psychosis (Johnstone et al, 2005; Miller et al, 2002; Yung et al, 2004). The development of paranoia and persecutory ideation follows the onset of social anxiety which serves the function of maintaining or strengthening persecution ideation. The work by Freeman et al (2005a; 2005b) has shown how common social anxieties, for example, fear of rejection, interpersonal sensitivity and negative beliefs about the self are amongst the most commonly reported types of suspiciousness (2005a) and form the basis upon which ideas of reference and more severe levels of paranoid thinking are established. Furthermore, these anxieties and social evaluative concerns were found to predict paranoid thinking in a non-clinical sample (2005b).

b. social anxiety and paranoia develop concurrently in the early phase of psychosis and follow a similar course

This pathway suggests that for a sub-group of individuals, social anxiety and paranoia may develop at the same time and follow a similar course. According to Freeman et al (2001), social anxiety and paranoia are underlined by common fears and concerns which refer to the anticipation of *threat* and danger which drives behaviours of avoidance and withdrawal from social interactions. It is expected therefore that for this sub-group of people, addressing paranoid concerns and ideas of persecution, would inevitably lead to the remission of symptoms of social anxiety and avoidance.

c. social anxiety may develop for some people as a consequence of paranoid beliefs

The third pathway suggests that for a sub-sample of people with psychosis, symptoms of social anxiety and avoidance may develop as a direct consequence of their paranoid ideation. Persecutory beliefs and perceived threat regarding other people's intentions to cause harm can lead to elevated social anxiety and apprehension during social encounters. As a way of protecting or "saving" oneself from such social threats, individuals may engage in safety behaviours by isolating themselves from the social world and actively avoiding all social interactions.

Following the findings of a thorough investigation into the psychological processes that underlie the emergence and maintenance of social anxiety in psychosis (Michail & Birchwood, 2012), a fourth potential pathway is provided here:

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d. social anxiety as a response to the shame and social stigma attached to a diagnosis of mental illness

In a recent study by Michail & Birchwood (2012), the authors examined the relationship between shame cognitions, shame proneness and perceived loss of social status in people with first-episode psychosis and social anxiety disorder. Findings showed that psychotic individuals with social anxiety expressed high levels of shame proneness which was accompanied by perceived loss of social status. They also reported significantly greater negative appraisals arising from a stigmatizing illness, including shame and fear of rejection, compared to their counterparts without social anxiety. These findings were consistent with those of earlier studies (Birchwood et al, 2007, Gumley et al, 2004) reporting that dysfunctional appraisals held by socially anxious psychotic people were characterized by shamefulness, humiliation and perceived rejection by others.

The authors proposed that individuals with psychosis are characterized by an established vulnerability to shame linked to early developmental anomalies. This shame proneness is likely to be catalysed by the stigma attached to the diagnosis of mental illness and there is evidence to suggest that psychosis is indeed considered as a highly stigmatized condition (Thornicroft et al, 2009). As with any type of *social stigma*, this can affect the social identity of the individual by suggesting qualities that deviate from the norm and are socially discrediting (Goffman, 1963). Individuals with psychosis are aware of the social stereotypes surrounding mental illness and some may even accept and endorse these (Hayward & Bright, 1997; Angermeyer et al, 2003). This internalization of stigma or *self-stigma* leads to increased shamefulness -particularly when individuals agree with the stigma and the associated negative responses (Corrigan & Watson, 2002a; 2002b)- and fear of the illness being revealed to others due to the consequences of this discovery (e.g. social exclusion, marginalization). Hence, the authors suggested that people with psychosis will attempt to conceal their stigmatized identity to prevent or minimise this threat by promoting behaviours of submissiveness or by avoiding and withdrawing from social interactions.

8. Clinical implications

There is lack of evidence on the clinical effectiveness and cost effectiveness of psychological interventions for the treatment of affective dysregulation and associated distress in psychosis. Cognitive behaviour therapy (CBT) is recommended for people with psychosis (NICE, 2009); however, its focus and evaluation has primarily revolved around the reduction of psychotic symptoms, and not for comorbid depression and social anxiety. Furthermore, psychological interventions such as CBT for the treatment of affective disorders in non-psychotic populations are proposed for the management of affective dysfunction when this is comorbid in psychosis (Halperin et al, 2000; Kingsep et al, 2003). This could be challenging as such treatments in order to be effective, would need to adapt to the specific nature of symptoms and difficulties experienced by people with psychosis (Tarrier, 2005). The findings of the recent study by Michail & Birchwood (2012) suggest that the "conventional" CBT

for social anxiety in psychosis could be considerably enhanced with an additional focus on shame cognitions linked to psychosis and accompanying concealment behaviours which are suggested to form part of the safety behaviour repertoire of socially anxious psychotic individuals. A randomised controlled trial testing the effectiveness of a CBT intervention in targeting shameful cognitions while reducing or eliminating concealment linked behaviours could be effective in psychosis.

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Chapter 8

Social Anxiety, Beliefs About Expressing Emotions and Experiencing Positive Emotions

Jasminka Juretić and Ivanka Živčić-Bećirević

Additional information is available at the end of the chapter

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1. Introduction

1.1. Social anxiety

Social anxiety refers to the excessive and persistent fear that a person will be embarrassed and/or rejected by other people in one or more social or performance situations [1]. When a socially anxious person wants to present a desirable image of him/herself, a strong desire to accomplish it is accompanied by considerable uncertainty if he or she can really do it. Almost every person has to some extent felt socially anxious (feeling weird, blushing or stammer) in some social situations or situations in which he or she has been evaluated.

People differ in how often and with what intensity they feel socially anxious and show a certain degree of consistency in how anxious they are across social situations and over time [2]. Thus, some people are by nature strongly and more frequently socially anxious then other and we are considering this as a feature of the personality. Leary and Kowalski [2] find that, despite different results, there is little reason for assuming that social phobia/social anxiety disorder is qualitatively distinct from social anxiety as personality trait. Socially phobic persons experience a stronger intensity of anxiety in social situations, their attempts to escape unpleasant social contacts are more extreme and anxiety they are experiencing seriously affects their everyday life. A number of studies show that social anxiety is a continuum, from complete lack of social fear, through the usual forms of shyness and mild social anxiety, to social fears that significantly impair functioning and lead to social anxiety disorder [3]. When social situations become extremely unpleasant to a person and he or she starts to avoid them significantly impairing his/her quality of life, then we are talking of social anxiety disorder [1].

The fact that social phobia often precedes and/or occurs in comorbidity with other psychiatric disorders [4] and is often inadequately treated, stresses the need for further research and

development of more efficient treatment [5, 6, 7]. When a person seeks professional help for many years after the social anxiety disorder has developed, it is possible that it has been primarily done because of symptoms related to other disorder/s.

Social anxiety disorder is a complex construct with which we try to describe a very heterogeneous group of people. It is important to distinguish people who are afraid of all or almost all social situations, from those who are afraid of only few of them. Likewise, it remains unclear whether the diagnostic subtypes are quantitatively different or reflect different qualitative entities of social phobia.

Studies have confirmed that at least two types of social anxiety should be distinguished: anxiety related to social interaction and anxiety related to some action performance. Anxiety related to social interaction consists of fears when meeting other people (e.g. initiating and maintaining conversation with other people, either in dyads or in groups), while performance anxiety relates to social evaluation concerns of doing something in front of other people (e.g. writing, playing an instrument, giving speeches) which the person would not be afraid doing if alone [8].

The role of cognitive processes and processes of focusing attention in the maintenance of social phobia are emphasized in contemporary theories [2, 9, 10]. According to these theories, extremely high standards of behavior in social environment maintain social phobia. These standards are characterized by negative thoughts, respectively statements of a person talking to him/herself and his/her assumption that other people see him/her as unsuitable, such as boring [9, 10]. In addition, socially anxious people consider beliefs and assumptions other people have about them as accurate and true. Consequences of these beliefs and assumptions are frequent negative self-statements, negative appraisal of their own behavior in social setting, increased self-focused attention on what has been done wrong in social interaction instead of focusing attention on those aspects which have been done well. Socially anxious people than become preoccupied with thoughts of how they would be evaluated by others and strongly shift attention to detailed monitoring and observation of themselves and impression they leave, including physiological symptoms of anxiety [9, 10, 11].

According to Clark and Wells [9, 11, 12, 13], when social phobics enter a feared situation, a set of assumptions (about themselves and their social world) is activated. If a person estimates situation as dangerous, so-called "anxiety program" is activated. The anxiety program includes physiological, cognitive, affective and behavioral changes that were designed to protect us from harm, but when the danger is largely overestimated this program loses its useful function. Anxiety symptoms, together with the strategies of coping with it, a person can misinterpret as sources of risk, which leads to an exacerbation of anxiety and a series of vicious circles that maintain social anxiety.

Several processes are important in development and maintenance of social anxiety [9]. One of the most important processes is the one concerning the self-focused attention. The shift in attentional focus happens to every social phobic – from perceiving the outside world to detailed monitoring and observation of oneself. The result is the construction of the self as a social object which helps creating an impression of how they appear to others. Onwards,

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entering feared situation, social phobics tend to use a wide range of safety behaviors they believe are helping them to prevent social disaster. Not only these behaviors are not helpful, they are also very harmful for social phobics. On one hand, safety behaviors can enhance feared behaviors and on the other, it prevents the person from perceiving any positive social feedback which might help in changing unrealistic beliefs. This means that unrealistic beliefs about feared behaviors or the consequences of these behaviors cannot be rejected. According to Clark and Wells, anticipatory and post event processing is very important; it contributes to the instability of self-image of social phobic person and in maintaining a high level of self-focused attention [11]. The basic feature of the anticipatory and post event processes is negativistic thinking concerning the extensive rumination about future failures or real or imagined past failures [14].

Besides importance of cognitive processes in developing and maintaining social anxiety disorder, it is also important to consider processes of emotion regulation. Many studies show that difficulties with emotion regulation are associated with psychopathology (e.g. 15, 16). It is necessary to explore the role of different ways of emotion regulation in development of specific disorders and to create models which integrate both cognitive and emotion regulation processes in development of psychopathology.

1.2. Emotion regulation

Through emotions we give other people information about our internal condition and behavioral intentions [17] and therefore they play an important role in interpersonal communication and our lives. They are manifested through specific cognitive, behavioral and physiological responses and are basis for adapting to new situations. If the person assess the situation as relevant to his or her goals and find it as an interesting one, then the emotions start to occur. Someone's goals may differ in many ways [18]. Goals may be enduring or temporary, conscious and complicated or unconscious and simple. They may be widely shared and understood or highly idiosyncratic. They may have a central role in understanding of ourselves or be peripheral. The base for developing an emotion is the meaning that a person gives to the situation. As the meaning changes over time, the emotion changes, too. Changes in emotional response can be triggered by situational changes or by the changes of significance that the situation has for the person [18].

Emotions occupy the whole body and include changes in the domains of subjective experience, behavior and physiological reactions. Impulses that encourage us to behave in certain ways and not act otherwise are associated with changes in the autonomic system and neuroendocrine changes. Those changes are followed by a particular behavior [18]. Because of a series of changes in various systems, emotions have imperative quality which means they can terminate the current activity and force a person to become aware of them. Also, when they occur, emotions often have to contend with other reactions that result from the same social context from which they have emerged. This is the most important fact for emotion regulation analysis because of the possibility to modulate emotions in many different ways.

Under certain circumstances, emotions have adaptive function; they have an evolutionary, a social and communicative and a decision making function [16] but they can also become a

source of dysfunction and be maladaptive. It is a challenge to find the way how to regulate our own emotions in order to retain emotional useful features, and to limit their damaging aspect. Emotions can hurt us if they occur at the wrong time or with wrong intensity [18]. The ability to successfully regulate emotions is very important because those inappropriate emotional responses are involved in many forms of psychopathology or in somatic illness development.

A process model of emotion regulation supposes that specific strategies of emotion regulation can vary over a sequence of development of emotional responses [19- 21]. This conception of emotion regulation implies that emotion emerges with an evaluation of emotion cues that can be either external or internal. When a person pays attention to these cues and evaluate them in a certain way, the emotional cues trigger a coordinated set of response tendencies involving experiential, behavioral and physiological systems. Once these reactions occur, they can be modulated in different ways. As emotion develops over a certain period of time, emotion regulation strategies may differ by the point in the emotion-generative process at which they have their primary impact.

A process model of emotion regulation [19, 21- 23] highlights five families of emotion regulation strategies: situation selection, situation modification, attentional deployment, cognitive change and response modulation. Processes related to first four families are considered as *antecedent-focused* because they occur inclusive with appraisal based on which a complete emotional response will be created. In contrast, emotional regulation that is focused on response modulation is called *response-focused,* as it occurs after emotional response tendencies are activated (physiological, experiential and behavioral).

There are clear individual differences in preferred ways of emotional regulation which is important in predicting the behavior of other people [24]. It is shown that people who react better on life demands are the one able to recognize their own emotional states, to understand the meaning of emotions and use their informational value, as well as to adjust the expression of emotion and their own response in a way that fits the context of the situation. This set of abilities is often called emotional intelligence [25].

Suppression is one of the most widely studied emotion regulation strategies. It is a response-focused emotion regulation and refers to attempts of ignoring already generated emotions and avoiding their expression [21]. Suppression is a way to regulate emotions after cognitive reappraisal of emotional content, respectively it comes relatively late in the emotion-generative process after the behavioral tendencies have been initiated [19- 22]. Studies have shown that this way of emotion regulation is counterproductive because it actually leads to a paradoxical reinforcement of physiological arousal and unwanted affect itself [26]. Suppression of negative emotions brings no relief in sense of its subjective experience [22]. It also leads to decreased expression of both positive and negative emotions and is considered to interfere with relationships triggering unpleasant reactions in other people [20]. This emotional regulation strategy is associated with rare experience of positive emotions and their seldom expression [21, 24, 27].

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Although suppression is generally considered to be a maladaptive emotion regulation strategy, it can be adaptive in situations where revealing emotions (e.g. anger or anxiety) should be restrained [28] or optimum distance between people should be maintained in order to facilitate a smooth social interaction [29].

1.3. Beliefs about expressing emotions

The way a person will regulate her or his emotion is strongly affected by beliefs she or he has about emotions [30]. If a person does not believe that efforts to regulate emotions will be successful, she or he will consider her/himself incompetent and uncertain and will invest a little effort and energy into implementing strategies of emotional regulation. In contrast, people who believe that emotions can be changed and controlled will be effective in regulating emotions using different adaptive strategies. Beliefs about emotions and emotional expression mediate the relation between experiencing emotions and there expression and thus have impact on emotion-generative process.

Negative reactivity to emotions refers to negative beliefs a person has about emotions, such as fearing consequences following emotion [25]. This construct applies to discomfort when experiencing emotions which leads to strong beliefs that emotional responses are dangerous and harmful for a person.

It has been assumed that socially anxious individuals may refrain from expressing their own emotions to avoid potential rejection. Refraining from expressing emotions offers less "material" for observation, which may cause rejection by others. Studies have shown that socially anxious people indicate a stronger suppression of their emotional experiences, they have lower capacity to monitor, differentiate and describe their own emotions and have more fears related to the experience of emotion and loss of control over them [31]. Spokas, Luterek and Heimberg [31] have found that beliefs about expressing emotions are significant mediators in the relationship between social anxiety and suppression of emotion, after controlling the effect of social phobics' ability to describe their own emotions to other people and their capacity to monitor them.

Tamir et al. [32] have confirmed that people who believe emotions are adaptable and changeable shape their own emotions by changing the evaluation of events that caused them. Regardless of the beliefs about emotions people have, they have an equal probability of masking their own feelings in certain situation. Those who believe in the malleability of emotions do not have fixed habit to use suppression as emotional regulation strategy.

1.4. Social anxiety, experiencing positive emotions and quality of life

Although inconsistent, positive emotions can have a lasting impact on our functioning through improvement of our well-being and relations with other people [33]. Research shows that induced positive emotions increase the personal feeling of unity with a close person and increase the confidence that we have in acquaintances. Likewise, the experience of positive emotions expands our attention and reflection in the field of personal and interpersonal functioning.

Other people and interaction with them are the source of positive events and emotions and therefore social activities and a sense of connection with other people are very important for our well-being [34]. There are also clear social benefits from sharing pleasant social events with other people, as they can be attributed to the relationship itself and thus reinforce social ties [35].

Social phobics are overly focused on the negative outcomes which interfere with their ability to recognize and respond to the potential rewards that come from the environment. It is expected that they experience high levels of negative affect and very low level of positive affect when anticipating participation, participating or constantly thinking about participating in social situation [36].

The current models of anxiety and depression (e.g., 37) generally assume that only depression is associated with deficits in positive emotions and events. Recent studies show that this deficit is also associated with social anxiety (e.g. 3, 36, 38). Socially anxious people have decreased positive affect and other positive psychological experiences (e.g., curiosity), even after controlling depressive symptoms, and have less frequent and less intense emotional response to positive social events [39]. They report about experiencing less frequent daily positive emotions and events than nonanxious people, and it could not be attributed to the conceptual overlap of social anxiety and other negative affective states [40]. The results have also shown that social phobics reported less positive events experienced during those days when they experienced higher levels of social anxiety and when tended to suppress emotions.

There is a strong evidence of correlation between social anxiety and reduced positive experience [3]. Social anxiety explained an additional 4-5% of variance in positive experiences, after controlling for depression, which is important in understanding this relationship. In his meta-analysis a stable inverse relationship between social anxiety and positive affect has been found (r=-.36; 95% confidence limits (CI): -.31 to -.40) and it remains even after the variance attributed to depressive symptoms and disorders is removed.

It has been found that especially those aspects related to social interaction are related to low positive affect [8]. The significant and negative association of anxiety related to social interaction with all domains of positive psychological functioning, after controlling neuroticism, has been found [36], while anxiety and fear of being observed by others did not show significant association with these domains.

Social anxiety as a trait is negatively correlated with daily episodes of happiness, relaxation, and positive emotions in general and positively correlated with anger [41]. Results confirmed diminished experience of positive emotions and increased experience of anger in individuals with relatively high levels of social anxiety regardless of being alone or with other people. The authors believe that these two emotional experiences are potentially relevant to socially anxious people.

Socially anxious people express less positive emotions, overall pay less attention to their emotions and have more difficulty in describing their emotions than those with generalized anxiety disorder and control non-anxious group [42]. They express greater fear of anxiety, sadness, anger and even of positive emotions then control group. Insufficient attention to

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emotions or their frequent ignoring can contribute to difficulties that social phobics have in raising awareness and recognizing their own emotions and in understanding why they feel the way they do. Individuals who are able to recognize and use their emotions are better prepared to flexibly and adaptively respond to environmental requirements and appropriately regulate their affect [43].

Further studies of relationship between social anxiety and positive emotions are needed. It is well known that positive emotions induce more rapid recovery from adverse physiological effects of negative emotions, increase awareness during activity, efficacy and quality in decision making process and access to more creative and more flexible options in a particular situation [35]. Thus they have impact in life quality which has been found to be impaired in socially anxious people.

In order to understand better the relationship between social anxiety and experiencing positive and negative emotions and life satisfaction in general, the new model has been proposed and tested. Based on the model of social phobia [9], which emphasizes the role of cognitions, and process model of emotion regulation [20], especially the response modulation, proposed and tested model has included relationship between social anxiety (two dimensions: general fears and avoidance behaviors concerning social interactions and social evaluation concerns/anxiety related to being observed by others), beliefs about emotional expression, emotion suppression, positive and negative emotions and life satisfaction in general, controlling for depressive symptoms and neuroticism. It is assumed that the relationship between social anxiety and experiencing emotions and life satisfaction in general will be mediated by beliefs about expressing emotions and emotion suppression.

The further aim of the study was to test an interaction effect of social anxiety (with control of neuroticism and depression) and emotion suppression in explaining the frequency of experiencing positive and negative emotions.

2. Method

2.1. Participants

The sample consisted of 521 female students attending University of Rijeka and University of Pula, in Croatia. The average age of participants was 21.21 (SD = 2.5 years; range 18-37).

2.2. Instruments

To assess personality traits, The Big Five Inventory was used [44]. It provides a good coverage of all five personality traits (Extraversion, Agreeableness, Conscientiousness, Neuroticism and Openness), and has satisfactory psychometric properties. Inventory consists of 44 items, using five-point Likert-type format for answers scoring. For the purposes of this study only Neuroticism subscale was used (8 items). Cronbach-alpha for the present sample was .81.

Beck Depression Inventory-II [45] has been used to assess depressive symptoms. It is a 21-item self-report scale, using four-point Likert-type format (higher number meaning more severe depressive symptom). Cronbach-alpha in this sample was .90.

Anxiety in social interaction was assessed using Social Interaction Anxiety Scale [46] and fear of being observed and evaluated by others using Social Phobia Scale [46]. Both self-report scales consist of 20 items each, using five-point Likert-type format for scoring the answers. Cronbach-alpha for SIAS was .90 and for SPS .91.

Emotion Regulation Questionnaire [21] was used to assess emotional regulation strategies – reappraisal and suppression. For the purposes of this study only Suppression subscale was used. It consists of 4 items measuring the tendency to inhibit or conceal emotional expression that a person has experienced. Answers are scored by using seven-point Likert-type format. Internal reliability coefficient (Cronbach-alpha) for this subscale on the sample of participants of the present study was .74.

Attitudes Towards Emotional Expression Questionnaire [47] is constructed to measure negative beliefs and behaviors related to emotional expression and in the present study are used to assess beliefs about emotional expression. It is a 20-item self-report scale, using five-point Likert-type format for answers scoring. In the original form, the questionnaire consists of four factors: beliefs about meaning (sign of weakness), beliefs about expression (keep in control), beliefs about consequences (social rejection) and behavioral style (bottle up). The present study did not confirm these four subscales, but the authors recommended that subsequent research should focus on subscales as well as the overall scale. In the present study two factors were extracted, each of them with 10 items. The first factor is composed of items that are in the original questionnaire related to beliefs that expressing emotions is a sign of weakness, and beliefs that expressing emotions lead to social rejection. This factor is, therefore, called *the belief that expressing emotions leads to unpleasant consequences*. The second factor is composed of items that are in the original structure of the questionnaire related to the belief that it is important to have an expression of emotions under control and of items related to behavioral tendency to suppress the expression of emotion. This factor is called *the belief that emotions should not be expressed*. Cronbach-alpha for each subscale was .87.

To measure the subjective experience of emotion, Positive and Negative Affect Schedule – Expanded Form [48] has been used. This is a 20-item inventory that consists of 10 adjectives measuring positive affect (e.g. cheerful) and 10 adjectives measuring negative affect (e.g. irritable). Answers are scored by using five-point Likert-type format. Cronbach-alpha for positive affect subscale was .85 and for negative affect subscale .87.

In order to assess how a person is satisfied with her life, a Satisfaction with Life Scale [49] has been used. It is a 5-item self-report scale, using seven-point Likert-type format for answers scoring. Cronbach-alpha in the present sample was .86.

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2.3. Procedure

Data were collected during classes in group format, anonymously. Goal of the study was briefly explained and students participated voluntarily. The students who were not willing to participate were allowed to leave the room.

3. Results

In order to determine the relationship between the variables involved in the study, correlation analyzes have been performed. Pearson's correlation coefficients are shown in Table 1.

	Fear of being evaluated by others	**Belief – expressing emotions leads to unpleasant consequences**	**Belief – emotions should not be expressed**	**Suppression of emotions**	**Positive emotions**	**Negative emotions**	**Life satisfaction**
Anxiety in social interactions	.74**	.45**	.29**	.28**	-.30**	.52**	-.40**
Fear of being evaluated by others		.41**	.21**	.18**	-.21**	.53**	-.38**
Belief – expressing emotions leads to unpleasant consequences			.64**	.48**	-.15**	.39**	-.31**
Belief – emotions should not be expressed				.75**	-.14**	.14**	-.18**
Suppression of emotions					-.15**	.12**	-19**
Positive emotions						-.17**	.43**
Negative emotions							-.43**

**p <.01

Table 1. Correlations between variables involved in the proposed model

According to results, if a young woman has a higher anxiety in social interactions, she will have increased fear of other people's evaluation. Socially anxious person will believe that emotions should not be expressed and that their expression leads to unpleasant consequences so will suppress emotions and will experience negative emotions more often. Such a female experiences positive emotions also less frequently and is less satisfied with her life. The belief that expressing emotions leads to unpleasant consequences and that emotions should not be expressed are highly positively correlated with each other, and are positively correlated with suppression of emotions and more frequent experience of negative emotions. Both beliefs are negatively correlated with life satisfaction and positive emotions. A female who uses a strategy of suppressing emotions as a way of emotion regulation, has lower life satisfaction and less frequently experiences positive but more often negative emotions. Frequent experience of positive emotions means less frequent experience of negative emotions and greater satisfaction with life, while often experiencing negative emotions means less satisfaction with life in general.

In order to determine the unique relationship between social anxiety and other variables in further analyzes, a common variance of social anxiety shared with neuroticism and depression is controlled. The aim was to eliminate the possibility that the potential negative effects of social anxiety, primarily in experiencing positive emotions, can be attributed to a common variance, or negative affectivity, which is shared by social anxiety, neuroticism and depression, and not to the uniqueness of social anxiety. Certain models suggest that neuroticism as a higher common vulnerability factor explains most of the covariance among the more specific constructs such as social anxiety, depression and anger [36]. It is considered that there are unique characteristics of high social anxiety that are not part of neuroticism. In order to control neuroticism and depression, regression analyzes were performed with standardized residuals calculated for both types of social fears. In regression analysis, the predictors included neuroticism and depression. Fear of social interaction was a criteria in the first analysis and a fear of being evaluated by others in the the second. After that the standardized values for both types of social fears were calculated. In this way we got two new variables, which were used for further analysis and in which negative affectivity related to neuroticism and depression is excluded, and only the part that is associated with a particular social fear has remained.

A variety of statistical analyzes were conducted in order to answer the research questions. The results were processed using the program LISREL 8 [50] and SPSS 15.0 for Windows.

3.1. Testing the model

The tested model included the relationship between both types of social fears, beliefs about expressing emotions, suppression of emotions and frequency of experiencing positive and negative emotions and life satisfaction.

The theoretical model is shown in Figure 1. Only significant direct and indirect effects are shown.

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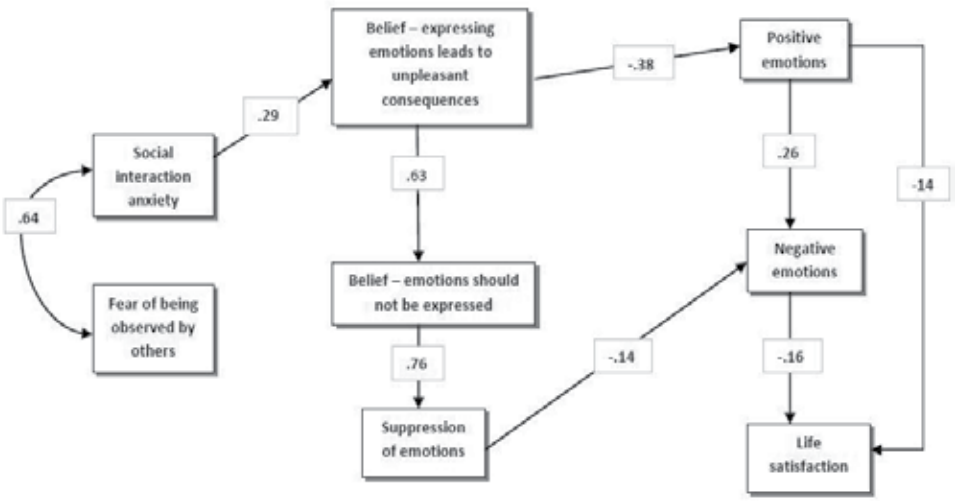

Figure 1. The model of relations between social anxiety, beliefs about the expression of emotions, suppression of emotions, experiencing positive and negative emotions and life satisfaction

Model fit indexes for this model are shown in Table 2.

	χ^2	degrees of freedom	χ^2/ degrees of freedom	RMSEA	GFI	NFI	CFI
Model	83.52***	19	4.39	0.09	0.96	0.93	0.95

***< p.001

Table 2. Fit indexes for theoretical model compared with empirical data

The indexes shown in Table 1. indicate that this model is acceptable. Chi-square index is significant, but it is affected by sample size and for large samples is generally significant. To reduce sensitivity of model chi-square to sample size, ratio chi-square and degrees of freedom have been calculated. This ratio indicates that the model is acceptable as well as RMSEA value. The values of GFI, NFI and CFI show that the model has a good fit with empirical data.

In this model, the fear of other people's evaluation does not have direct or indirect effects on remaining variables included in the model. Anxiety in social interactions has only a direct positive effect on the belief that the expression of emotions leads to unpleasant consequences (.29), while other effects of this variable, except the one mentioned, are mediated by the belief that emotions should not be expressed and by suppression of emotions. The belief that expressing emotions leads to unpleasant consequences have a direct, positive and strong effect on the belief that emotions should not be expressed (.63) and moderate, negative and direct effect on positive emotions (-.38). The belief that emotions should not be expressed has a direct, high and positive effect on the suppression of emotions (.76), which has a direct negative effect

on negative emotions (-.14). Positive emotions have a direct positive effect on negative emotions (.26) and negative on life satisfaction (-.14). Negative emotions have a direct negative effect on life satisfaction (-.16).

According to obtained results it is evident that the effects of social anxiety on the experience of positive and negative emotions and life satisfaction are achieved indirectly through beliefs about emotional expression and suppression.

3.2. The contribution of interaction effect of social anxiety and suppression of emotions to the frequency of experiencing positive and negative emotions

In order to test whether there is an interaction effect of social anxiety (with control of neuroticism and depression) and suppression of emotions in explaining the variance of experiencing positive and negative emotions after determining the individual contributions of both types of social anxiety individually and suppression of emotions, hierarchical regression analyzes were conducted.

Four hierarchical regression analyzes were conducted. As the first step, anxiety in social interactions has been included in the first two analyzes, and the fear of other people's evaluation in the other two. In each of the hierarchical regression analyzes the suppression of emotions has been included in the second step. In the third step the interaction of anxiety in social interactions and suppression has been included in the first two analyzes, and interaction of fear of other people's evaluation and the suppression in the other two. For each analysis there were two criteria - positive and negative emotions.

Results are shown in Tables 3. and 4.

positive emotions									
predictors	**R^2**	**ΔR^2**	**F-change**	**β**	**predictors**	**R^2**	**ΔR^2**	**F-change**	**β**
1.step anxiety in social interactions	.03	.03	12.72***	-.13**	1.step fear of being evaluated by others	.00	.00	1.21	-.03
2.step suppression of emotions	.05	.02	9.67**	-.15**	2.step suppression of emotions	.03	.03	13.86	-.17***
3.step anxiety in social interactions x suppression of emotions	.05	.00	.02	.00	3.step fear of being evaluated by others x suppression of emotions	.03	.00	.00	.00

** p<.01; *** p<.001

Table 3. Results of hierarchical regression analyzes for positive emotions as criteria

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The results of hierarchical analysis which includes anxiety in social interactions show that included variables explain only 5% of the variance in frequency of experiencing positive emotions. Anxiety in social interactions explains 3% of the variance of criteria and suppression of emotions 2%, while the interaction of these two variables does not explain the frequency of experiencing positive emotions. Both anxiety in social interactions and suppression of emotions are negative predictors.

The results of hierarchical analysis which includes fear of being evaluated by others showed that only 3% of variance in frequency of experiencing positive emotions is explained, while suppression of emotions is the only significant and negative predictor.

negative emotions									
predictors	**R^2**	**ΔR^2**	**F-change**	**β**	**predictors**	**R^2**	**ΔR^2**	**F-change**	**β**
1.step anxiety in social interactions	.04	.04	18.27***	.17***	1.step fear of being evaluated by others	.04	.04	21.65***	.20***
2.step suppression of emotions	.05	.01	3.51	.09	2.step suppression of emotions	.05	.01	4.83**	.10**
3.step anxiety in social interactions x suppression of emotions	.05	.00	.24	.02	3.step fear of being evaluated by others x suppression of emotions	.05	.00	.04	-.01

** p<.01; *** p<.001

Table 4. Results of hierarchical regression analyzes for negative emotions as criteria

The analysis with the anxiety someone is experiencing in social interactions, included in the first step, showed that only this variable is significant and positive predictor of the frequency of experiencing negative emotions and it explains 4% of the variance. Additional 1% of variance is explained by suppression of emotions as a strategy of emotional regulation, but as well as interaction included in the third step, it is not a significant predictor in the analysis.

The other conducted analysis showed that included variables explain only 5% of the variance in frequency of experiencing negative emotions. The fear of being evaluated by others and suppression of emotions are the only significant and positive predictors, while the interaction effect of these two variables is neither significant nor does it additionally explain the frequency of experiencing negative emotions.

4. Discussion

When presented model for the presumed relations was tested, only social anxiety that refers to the fear that a person experiences during encounters with other people (e.g. initiating and maintaining conversations either in dyads or in groups) was found significant. As previous studies revealed its role in experiencing positive emotions, it was expected for this aspect of social anxiety to be significant [3, 10, 35, 36, 38, 40]. The second type of social anxiety, the one related to fear of being observed and evaluated by others, has not been studied enough in previous research. Although it was expected that, as a social fear, it could have had some effects on other variables, it was not proven. There is a possibility that this kind of fear is not so important in comparison with anxiety felt during social interactions.

Anxiety in social interactions did not show the expected direct effects. In the first place there was no direct effect on the beliefs that emotions should not be expressed and on their suppression. Its relationship with these variables is only indirect through belief that expression of emotions leads to unpleasant consequences with high and positive effects. This kind of relationship would mean that the suppression of emotions in a socially anxious woman occurs when she has a strong belief that expressing emotions leads to unpleasant consequences, due to which the belief that emotions should therefore not be expressed will be activated, which will result in her scruple of expressing any emotion (emotional suppression). The importance of our beliefs in the process of emotion regulation is confirmed by these results. Cognitive model [9] assumes that when an individual finds him/herself in a particular social context, negative assumptions concerning the assessment of the situation as dangerous will be triggered. In this way a whole series of negative automatic thoughts about themselves and other people are triggered. The finding that the beliefs about expressing emotions have an indirect role in relation of social anxiety and suppressing emotions stresses the significant role of cognitions. It seems that the belief that expressing emotions leads to unpleasant consequences is "superior" to the belief that emotions should not be expressed. This result is not unusual because if someone believes that it is not good to express emotions, he or she must have a direct or an indirect experience that emotion expression has led to unpleasant outcome. Unpleasant consequences are related to the belief that expressing emotions is a sign of weakness, which means that the one expressing emotions will be perceived as weak by others. Evaluating someone as a weak person means a specific trait or flaw because it is expected that an adult must be able to effectively and appropriately regulate his or her own emotional expression. Those who can control emotions and know how not to express them are estimated as powerful, while those who aren't successful in it tend to be estimated as weak, possibly even less desirable as friends and partners.

Although someone's fear of being evaluated and perceived as weak is in the first place related to the aspect of emotion regulation, we might draw a parallel to research [7] which dealt with the fundamental fears that social phobics experience. One of the four dimensions of stimuli evaluation that elicit social fear refers to the fear of socially anxious individuals to be seen with some character flaws. Moscovitch [7] believes that this aspect can be represented with statements like "I'm boring", "I'm stupid", with activities in which there is a disclosure of

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personal information (e.g. talking one on one) and with those in which these features are being questioned (e.g. telling jokes). According to his model, social phobics are afraid that their features, in fact themselves, in the eyes of others might be seen as incomplete in comparison to other people. It carries certain consequences of which they are afraid. Unpleasant consequences are related to other people's negative evaluation and rejection, embarrassment, loss of social status and likewise, which is neither pleasant nor desirable. For the same reason, an individual will resort to a number of safety behaviors. Being afraid of ranking as socially undesirable person supports the belief that expressing emotions leads to unpleasant consequences which clearly leads to belief that it is better to be emotionally restrained and, ultimately, to emotional suppression. Since socially anxious people simultaneously feel desire to approach other people but are afraid of rejection, strategy of suppressing emotional expression and adherence to the belief that expressing emotions leads to unpleasant consequences seems, from their perspective, a wise strategy to maintain social status. This mode of emotion regulation is used with intention to reduce the likelihood of experiencing a single unpleasant consequence. It is actually a paradox since the suppression of emotions is counterproductive, as it does not reduce unwanted, unpleasant experience and even strengthen physiological arousal [20- 22, 24, 26, 27, 51].

Anxiety in social interactions has only indirect effects on positive and negative emotions. The effect on positive emotions is realized over the belief that expressing emotions leads to the unpleasant consequences. Its effect on negative emotions is achieved through the emotional suppression (with previous indirect role of beliefs about expressing emotions). If a woman believes that expressing emotions is not good because it will lead to unpleasant consequences, she rarely experiences positive emotions. When she decides to suppress her emotions, it leads to increased incidence of experiencing negative emotions.

However, there are results that differ from the expected. It is found that the more frequent experience of positive emotions also leads to increased incidence of experiencing negative emotions and to overall life satisfaction reduction. This result might be due to low negative correlation (-.17) between experiencing negative and positive emotions, which was not expected when the emotions are measured in this way. When measuring the experiencing of emotions in a way that the participants are asked to indicate how they usually feel, there should be no correlation between positive and negative emotions [52]. Increased emotionality of the participants (emotional reactivity) may be the reason for such result. Emotionality indicates individual's predominant intensity of emotional reactivity which includes a person's tendency to overreact even to weak stressors [53]. Emotional reactivity was found to be associated with high blood pressure [54]. People differ in emotional reactivity and those who are emotionally more reactive are lacking in control over thoughts related to the emotional content and therefore emotions themselves. It is possible that the participants in this study are prone to experience and to express positive emotions, which in turn has an effect on the more frequent experience of negative emotions. Generally speaking, it is possible that these women are more likely to experience positive and negative emotions. Some authors also suggest that people, who experience intense positive emotions, also experience intense negative emotions [55].

It is also uncommon to find that the emotional suppression leads to less often experience of negative emotions, which is not in accordance with paradoxical effect of this emotion regulation strategy [20-22; 24, 26, 27, 51]. It is possible that, despite the strong impact of the emotional expression beliefs, our participants do not come up with enough strong tendencies to inhibit or to conceal emotions (M = 3.05).

As expected, it has been confirmed that more frequent experience of negative emotions leads to reduced global life satisfaction [56]. According to the hierarchical model of happiness [57], subjective well-being is related to cognitive and emotional components that are interconnected. Experiencing positive and negative emotions is emotional component and global assessment of life satisfaction refers to a cognitive component. According to *bottom-up* theories (deductive theories) [58], life satisfaction and happiness are the result of an individual's total number of happy moments in his or her life. In line with this notion of subjective well-being, a person is happy when experiencing a lot of happy moments, so the measure of general life satisfaction is derived through the sum of satisfaction in different life areas. This would mean that if a person is satisfied with certain areas of her or his life (e.g. partnerships, finance, etc.) then she or he gives higher estimation of global life satisfaction.

The obtained result that the more frequent experience of negative emotions leads to a reduced life satisfaction is in line with the assumptions on the assessment of quality of life, but the finding that more frequent experience of positive emotions has the same effect, certainly is not. As already noted, there are data on the intense experience of both positive and negative emotions [55] which can be related to the higher frequency of experiencing both of them. It turns out that the frequency of experiencing both positive and negative emotions have unfavorable effects on global life satisfaction for our participants.

It can be concluded that this model has provided additional insight into understanding the relationship between social anxiety, beliefs about the expression of emotions, suppression of emotions, and the experiencing of positive and negative emotions and the global life satisfaction in women. The main contribution of this model is the result of the role that cognitions play in these relationships. Their role is reveled over the beliefs about expressing emotions to other variables that confirmed the mediating role of these beliefs in relation to social anxiety and suppression of emotions [31]. It has also been found that only aspect of social anxiety which refers to the anxiety experienced in social interactions has significant effects in these relations.

A further objective of this study was to examine whether there is an interactive effect of social anxiety (with control of neuroticism and depression) and suppression of emotions in explaining the frequency of experiencing positive and negative emotions after determining the individual contributions of each type of social anxiety and of emotion suppression. The starting point for setting this problem has been the assumption that severe social anxiety can become an even bigger problem if there are rigid tendencies in mastering and concealing emotional experiences [35]. The authors were primarily concerned with the relationship of one aspect of social anxiety, the one that refers to the anxiety experienced in social interactions, and experiencing positive emotions, so this paper aims to determine the contribution of other type of social fear (fear of other people's evaluation) in experiencing positive and negative emotions. Although the research is primarily focused on understanding the experience of positive

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emotions in socially anxious women, contribution of both types of social fears and the suppression of emotions and their interaction effect on negative emotions has been tested.

The results of the hierarchical regression analyzes reveled that the interaction effect of social anxiety and suppression of emotion was not significant in explaining the frequency of experiencing neither positive nor negative emotions. This result does not support the theory about the interactional effects of these two variables on the expression of positive emotions [35], although the authors themselves have failed to confirm the „joint vulnerability" model. The reason for this result may lie in the fact that women who participated in this study were low in social anxiety and suppression of emotion was not their main emotion regulation strategy (anxiety in social interactions M = 0.89, SD = 0.59; fear of other people's evaluation M = 0.73, SD = 0.61; suppression M = 3.05, SD = 1.22). It is possible that this result is a consequence of experiencing low frequency (or at least the reporting of it) of positive (M = 3.29, SD = 0.61) and negative emotions (M = 2.09, SD = 0.56), which again is the issue of emotional reactivity of the women involved in this research.

Only social fear related to anxiety experienced in social interactions was a significant predictor of the frequency of experiencing positive emotions. Expression of this type of fear contributes to less often experience of positive emotions. The results are consistent with findings about negative role of social anxiety in experiencing positive emotions (e.g. 3, 36). However, the role of anxiety in social interactions was confirmed, and the fear of other people's evaluation shows no significance in studying positive emotional experiences. Relationships with other people are very important for our welfare, and positive events and emotions are important for the development of such relations. Mastering fear of social interaction is important for the ability to develop relationships with other people and, to some extent, precedes fear of the other people's evaluation which could emerge after the contact. In this study, fear of other people's evaluation mostly includes evaluation of foreigners and people who are not emotionally important to us (which does not diminish the importance of this type of evaluation for socially anxious people). Women in this study are not diagnosed as socially anxious, so it is possible that this fear does not interfere with their relationships with other people as far as the fear of interaction with them do. The presence of other people is important for the frequency of experiencing positive emotional experiences, and if this fear is prevalent, the opportunity for such experiences is reduced.

Suppressing was found as a negative predictor of the frequency of experiencing positive emotions, which means that the use of this strategy of emotion regulation contributes to less often experience of positive emotions. The result is consistent with the finding that the suppression of emotions leads to decreased expression of both positive and negative emotions, thus interfering with relationships with other people [20] and that this strategy is associated with rare experiencing positive emotions and their seldom expression [21, 24, 27]. Suppression of emotions was significant predictor of experiencing negative emotions, but only in the analysis which included fear of other people's evaluation as a predictor. Selecting this emotion regulation strategy means more frequent experience of negative emotions. The result is consistent with previous studies that have found this mode of emotion regulation as counter-productive because it leads to paradoxical reinforcement of physiological arousal and un-

wanted affect itself [26], and the suppression of expressing negative emotions does not bring any relief in terms of the subjective experience of negative emotions [22].

Women who have expressed any of the two types of social fears experience more frequent negative emotions which is consistent with previous results. Anxiety disorders are associated with exaggerated and persistent negative emotions [59] and the relationship between social anxiety and frequent experience of negative emotions is confirmed in a number of studies (e.g. 3).

Results of this study showed that only anxiety in social interactions explains the experience of positive emotions with only 3% of the variance explained. In his meta-analysis Kashdan [3] also found that social anxiety explains 4-5% of the variance in positive experiences after controlling depression. Our study went a step further by controlling neuroticism as a personality trait, which would certainly „blur" independent contribution of social anxiety in explaining the experience of positive emotions. The data of this study provide significant contribution, showing that social anxiety has its own independent role in understanding the reduced experience of positive emotions, and that it cannot be attributed to effects of depression and neuroticism.

It was found that both types of social fears have a significant role for experiencing negative emotions and that each could explain 4% of the variance of frequency of experiencing negative emotions. This finding confirms and emphasizes the independent role of social anxiety in more frequent experiencing of negative emotions because effects of depression and neuroticism are controlled.

The results of this study should be considered within the context of its limitations. First, the study is based on participants' self-assessment. While this is the most common method of data collection, for this type of research it is important to use a clinical sample of socially anxious people who use different strategies of emotion regulation. In order to comprehend better this set of problem, experimental design would have been a better solution to answer the research questions. However, the results of previous studies have shown different ways of regulating emotion in the laboratory experiments and those implemented in everyday circumstances, so it would be better to implement this type of research in everyday circumstances of socially anxious individuals. Such research would better succeed to grasp impairment of social functioning in relation to emotional regulation strategies, as well as effects on close relationships.

Further limitation is the fact that only women participated in the study. Because of gender differences in the severity of social anxiety and ways of regulating emotions, future research should check the same model in a male sample and compare models for both sexes.

The sample included only those participants who agreed to participate in the study and who, on average, were not socially anxious. It is possible that some women who decided not to participate in the research were more socially anxious and their results would be valuable in the study of relationships of social anxiety and other variables. Research on a clinical sample of socially anxious women whose daily functioning is disrupted by disorder could be especially useful and might give different results.

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Future research should focus on examining individual differences in emotional reactivity and sensitivity when studying the relationships that are examined here. As this study deals only with one of the strategies of emotion regulation - suppression, it would be important to test the model with reappraisal as emotion regulation strategy. This strategy has been found as adaptive and, as our data indicate the importance of cognitions in relationship between social anxiety and suppression of emotions, it would be important to see their relations when using this cognitive strategy of emotion regulation.

Considering that dimensions of social anxiety and emotion regulation are important for creating our relationships with others, future research might include assessment of quality of close relationships in the model. It was found that emotion regulation strategies have different effects on memory, and through the memory contents that are related to interpersonal relationships on the quality of close relationships [24, 60].

Practical contributions of this research are also worth mentioning. The results point out the importance that beliefs about emotions and their expression have on suppression of emotion, and experiencing emotions in general. Since these are dysfunctional beliefs that the expression of emotions leads to unpleasant consequences (to which a person does not want to be exposed), and due to which the belief that emotions should not be expressed is activated, the therapeutic work should focus on restructuring such beliefs about danger of emotions and their expression. On the other hand, the expression of emotions is important in interpersonal relationships. In development of quality close relationships it is necessary to mutually share emotional experiences which does not occur if someone perceives it as threatening. Therefore, it is important to teach socially anxious people about adaptive strategies of emotion regulation and to point out benefits, advantages and disadvantages of using different strategies. However, as the emotion regulation strategy is only a part of the entire system of self-regulation, it would be useful to check the person's capacities for self-regulation in general.

5. Conclusions

In conclusion, the results of this study have provided more insight into the complex relationship between social anxiety, emotional experiences and the quality of life in general. The mediation mechanisms that play a role in these relationships have been revealed by structural modeling, which has not been done in previous researches.

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Chapter 9

Co-Morbid Anxiety and Physical Disorders: A Possible Common Link with Joint Hypermobility Syndrome

Guillem Pailhez and Antonio Bulbena

Additional information is available at the end of the chapter

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1. Introduction

As we stated in a previous book chapter titled "Somatic conditions intrinsic to anxiety disorders" [1], Johann Christian August Heinroth (1773-1843) was the person who introduced for the first time the term 'psychosomatic' into medical literature. The psychosomatic approach offers an overall or holistic "body and mind" perception that can be often useful for prevention purposes. Unfortunately, up to the present day Heinroth's contributions to the development of medicine and psychosomatics have been little acknowledged. Possibly, the current medical tendency towards specialisation makes it difficult to embody such paradigms in current psychiatric and medical nosology.

In this sense, the group of anxiety disorders have been included alternatively among the somatic and among the mental conditions when, in fact, anxiety disorders include both strong somatic and mental dimensions which need to be dealt with. The study of somatic conditions linked to anxiety disorders provide insights into the biology of these mental disorders that may result in a greater understanding of its aetiology, treatment, and prevention. In this second chapter we shall review, up to the last findings, the comorbidity of anxiety and physical disorders linked to joint hypermobility syndrome (JHS). This relationship is one of the strongest available evidences of the somatic components of anxiety disorders.

2. Anxiety disorders do relate to some somatic conditions

Patients with anxiety disorders often complain of somatic features, especially cardiac (tachycardia, chest pain), gastrointestinal (epigastric pain), and neurological complaints (headaches, dizziness, or presyncope), in emergencies and primary services [2-4]. This clinical

phenomenon helped to deepen into the study of differential diagnoses: are they symptoms of the primary anxiety disorder or are they symptoms of a comorbid physical illness? [5-7]. Besides, more recent research suggests a strong association between anxiety disorders and somatic conditions, although some authors emphasize the huge amount of published research about somatic conditions and depression in contrast to the few studies about the same relationship with anxiety disorders [8-10]. Furthermore, results from the National Comorbidity Survey-Replication (NCS-R) showed that various anxiety disorders had equal or greater association than depression with four chronic physical disorders (hypertension, arthritis, asthma, and ulcers) [11].

The more recent review articles about this relationship are organized according to medical illness specifically associated to anxiety disorders in several descriptive and analytic studies with clinical samples [2,3,9,12,13]. These reviews often include the following somatic conditions: irritable bowel syndrome, asthma, cardiovascular disease, cancer, chronic pain, vestibular and thyroid dysfunction, chronic obstructive pulmonary disease, and mitral valve prolapse. Some of the main general conclusions of these reviews are the following: 1) emerging evidence about the bi-directional relationship between anxiety disorders and medical illness suggests that they may be as important as depression [9]; 2) such associations provide important clues for understanding the neurobiology of anxiety disorders [2]; and 3) such associations are greater for panic disorder [12,3], worsening its identification, presentation and treatment [13].

Along this way, there are four studies relying on clinical samples that have shown higher rates of somatic conditions among patients with anxiety disorders (table 1). The first one was published in 1994. Rogers et al. examined the prevalence and characteristics of medical illness in 711 patients with present or past index anxiety disorders [14]. Patients were assessed using structured diagnostic interviews and the Medical History Form II. The rates of medical illness for all subjects were later compared with data extracted from an epidemiological sample. Results showed that patients with panic disorder had more reported medical problems than the general population, in particular, more ulcer disease, angina, and thyroid disease.

In 2003, Härter et al. studied the associations between anxiety disorders and medical illnesses in a total of 262 probands (169 cases with an anxiety disorder and 93 controls with no evidence of an anxiety disorder according to DSM-III-R criteria) [8]. Diagnoses were obtained based on direct interview (SADS) or family history information, and lifetime history of numerous medical illnesses was obtained. Results showed that patients with a lifetime anxiety disorder reported higher rates of several medical illnesses than did persons without anxiety. After controlling for the effects of gender, comorbid substance abuse/dependence and/or depression, significant associations were found between anxiety disorders and cardiac disorders (OR = 4.6), hypertension (OR = 2.4), gastrointestinal problems (OR = 2.4), genitourinary disorders (OR = 3.5), and migraine (OR = 5.0). A similar pattern was observed for probands with panic or generalized anxiety disorder.

In 2005, Sareen et al. examined the relationship between anxiety disorders and a wide range of physical conditions in a nationally representative sample. Data came from the

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National Comorbidity Survey (N=5,877). Physical disorders were assessed based on a list of several conditions shown to respondents. Results showed that anxiety disorders were positively associated with physical conditions even after adjusting for mood disorders, substance-use disorders, and sociodemographics. Among specific anxiety disorders, panic disorder and agoraphobia were more likely to be associated with cardiovascular disease and bone and joint diseases [10].

In 2008, in a case-control study carried out by our group [15] using retrospective data extracted from clinical records, patients with anxiety disorders showed higher risk of medical illnesses than patients without anxiety disorders. The aim of the study was to investigate the comorbidity between anxiety disorders and somatic conditions in three groups: patients with anxiety disorders (n=130) including panic disorder with/without agoraphobia and agoraphobia without panic attacks, patients from a primary care unit without any psychiatric disorder (n=150), and patients from a psychiatric service without anxiety disorders (n=130). Multivariate statistical logistic regression analysis showed that patients with anxiety disorders presented 4.2-fold increase in the risk of cephalea, 3.9 of cardiopathy, 3.8 of osteomuscular disorder and 2-fold increase in the risk of digestive diseases.

	Type	N	Data assessment	Main associations
Rogers et al. 1994 [14]	D	711	Structured diagnostic interview	Ulcer disease, angina & thyroid disease
Härter et al. 2003 [8]	CC	262	Direct interview & medical records	Cardiac disorders, hypertension, digestive problems, genitourinary disorders & migraine
Sareen et al. 2005 [10]	E	5877	List of several conditions	Cardiac disorders & bone and joint diseases
Pascual et al. 2008 [15]	CC	410	Medical records	Cephalea, cardiac disorders, bone and joint diseases & digestive problems

Table 1. Relationship between medical conditions and anxiety disorders. Basic features of studies reviewed. D, descriptive study; CC, case–control study; E, epidemiological study.

3. Measuring medical conditions in anxiety patients

Despite the significant prognostic and therapeutic implications derived from the comorbidity between mental disorders and medical conditions, there is a lack of measuring instru-

ments designed to quantify the physical health and disease in psychiatric population. Obviously, the use of these instruments in clinical settings is virtually absent. In this sense, our team developed, for over a decade, the Spanish version of the Cumulative Illness Rating Scale [16] designed for the assessment of medical conditions in general. The issues chosen for this instrument to assess illness severity were related to life-risk, functional disability and the need for treatment. Our group is now actively working on a variation of this scale, specially designed to detect medical conditions, including some functional diseases, on anxiety and depressive patients. Some of these functional diseases assessed are atopy and allergies, tensional headache and migraine, fibromyalgia, irritable bowel syndrome, dysfagia and dyspepsia, interstitial cystitis, sexual dysfunction, temporo-mandibular joint disorder, and chronic fatigue syndrome.

There are various hypotheses on how anxiety disorders and medical conditions may be related [14]. Medical illness may sometimes directly trigger the development of anxiety symptoms (e.g., cardiomyopathy or anxiety as a psychological reaction towards an illness), or mimic anxiety symptoms (e.g. pheochromocytoma). Conversely, anxiety disorders may sometimes directly trigger the development of somatic symptoms (e.g., angina in cardiovascular disease), mimic symptoms of a medical illness (leading to high costly procedures or inadequate treatment), or may contribute to the onset or exacerbation of certain somatic conditions (e.g., hypertension or gastric ulcer).

However, there is evidence that some medical conditions that are often comorbid with anxiety disorders could share a common genetic etiology [17-19]. For example, Talati et al. studied probands with diagnosis and family history of panic disorder (n=219), social anxiety disorder (n=199), or both (n=173), and 102 control subjects with no personal/family history of anxiety. Subjects were blindly interviewed with a diagnostic instrument and medical history was obtained via medical checklist and the family history screen [20]. They found that panic or social anxiety patients and their first-degree relatives were more likely to have interstitial cystitis, mitral valve prolapse and headaches, and this was hypothesized to be linked to a common genetic susceptibility. According to this hypothesis, several studies have shown a noticeable association between anxiety disorders (particularly panic/phobic cluster) and the joint hypermobility syndrome (JHS) [21-23]. This association has allowed a wider "body and mind" comprehension of anxiety disorders and has provided new clues in order to measure medical conditions in these patients.

4. Anxiety disorders and the role of collagen tissue

JHS is an inherited connective tissue disorder associated with a generalized collagen laxity and characterized by an increase of active or passive joint mobility. The condition was not described for the first time until fifty years ago by Rotés, when it was properly identified and associated to pathology of the musculoskeletal system [24]. In 1973, after an epidemiological study by Beighton et al., the syndrome gained general interest in the rheumatological field and began to be studied in a broader way, as a separate entity [25] (see Fig.1).

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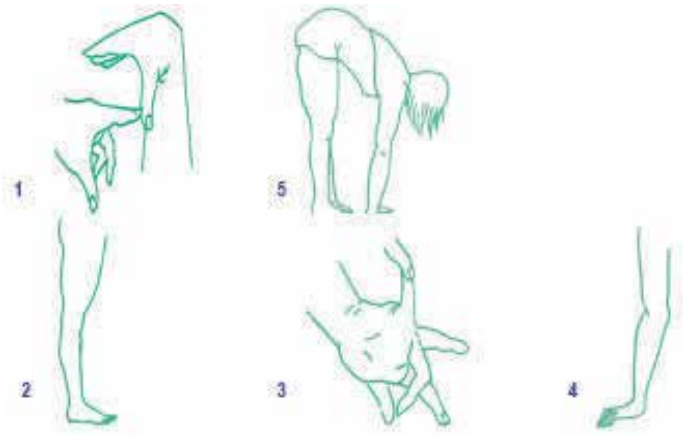

Figure 1. Joint Hypermobility criteria [25]1.Passive apposition of the thumbs to the flexor aspects of the forearm (one point for each thumb). 2. Hyperextension of the knee beyond 10º (one point for each knee). 3. Passive dorsiflexion of the little fingers beyond 90º (one point for each hand). 4. Hyperextension of the elbows beyond 10º (one point for each elbow). 5. Forward flexion of the trunk with knees fully extended so that the palms of the hands rest flat on the floor (one point).

In 1992, the Hospital del Mar criteria (table 2) compiled all the items included in the most clinically used criteria. This new scale showed consistent indicators of reliability, internal consistency and predictive validity, and provided evidence for using different scores according to age and gender [26].

Upper extremities
Passive apposition of the thumb to the flexor aspect of the forearm at a distance of less than 21 mm.
The passive dorsiflexion of the fifth finger is 90º or more.
The active hyperextension of the elbow is 10º or more.
External rotation of the shoulder up to more than 85º.
Lower extremities. Supine position
The passive hip abduction can be taken to an angle of 85º or more.
Hypermobility of the rotula.
Hypermobility of the ankle and foot.
Dorsal flexion of the toe of 90º or more.
Lower extremities. Prone position
Hyperflexion of the knee.
Ecchymoses.

Table 2. Hospital del Mar criteria for JHS [26]. Male patients scoring 4 or more are considered cases; female patients are considered cases with scores 5 or over.

JHS has an estimated prevalence in the general population ranging between 10% – 15%, it is more frequent among females (3:1) and is one of the hereditary disorders of the connective tissue, which include other conditions such as Ehlers-Danlos syndrome, Marfan syndrome and ostogenesisimperfecta [27]. Clinical features in JHS can be articular or extra-articular and are always related to the connective tissue. Among the best known articular features of JHS are arthralgia, lumbalgia, soft-tissue rheumatism (e.g., epicondilytis, tenosynovitis, bursitis), recurrent dislocations, childhood scoliosis, or rheumatoid arthritis [28,29]. Among the best-known extra-articular features of JHS are hernias, varicose veins, "easy bruising", keloids, uterine or rectal prolapse, spontaneous pneumothorax, fibromyalgia, dysautonomia and some other conditions also linked to panic disorder as asthma, mitral valve prolapse, thyroid dysfunction or irritable bowel syndrome [29,30]. Therefore, most of the conditions linked to anxiety disorders can be explained as clinical features of JHS. Unfortunately, the relationship between anxiety disorders and JHS is often neglected.

The clinical relationship between anxiety disorders and JHS was found 50 years ago. In 1957, the rheumatologist J. RotésQuerol pointed out for the first time the remarkable degree of nervous tension suffered by patients with hypermobility [24]. To a certain extent, there are some indirect references about the relationship between "hypotonia" and anxiety/phobias in the classical psychosomatic literature [31]. On the other hand, Carlsson and Rundgren in 1980 [32] found a higher score in hypermobility among alcoholic patients than among controls. Although not mentioned, the percentage of anxiety patients among the case group might have been high.

Empirical history of the clinical relationship between anxiety disorders and JHS starts in the case-control study conducted by our group in 1993, with rheumatologic outpatients affected by JHS [21]. Diagnoses of panic disorder, agoraphobia and simple phobia were significantly more frequent among hypermobile patients. There were no significant differences in the diagnoses of generalized anxiety disorder, dysthymia, or major depressive disorder. Around 70% of rheumatological patients with JHS had some kind of anxiety disorder. However, this only occurred in 22% of controls, a usual figure in chronic patient samples. Cases were 10 times more likely to suffer from anxiety than controls. Specifically, agoraphobia and panic disorders were, respectively, 5 and 7 times more likely (table 3).

	% JHS	% Non-JHS	Age-Sex Adjust. Odds Ratio	95 % C. I.
Any Anxiety D.	69,3	22,0	10.69	4.80-23.81
Panic D.	34.2	6.8	6.96	2.31-20.91
Panic & Agora.	24.6	5.1	6.40	1.82-22.43
Simple Phobia	29.8	8.5	5.77	2.05-16.24
Agoraphobia	37.7	11.9	5.08	2.06-12.49
General.Anx.	10.5	5.1	2.49	0.65-9.45
Major Depress.	14.9	3.4	4.51	0.99-20.56
Dysthymic D.	7.9	5.1	2.15	0.53-8.65

Table 3. Lifetime psychiatric disorders in JHS cases (n=114) and non-JHS controls (n=59) seen at an outpatient rheumatological unit [21].

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For a subsequent second study, conducted to support this hypermobility-anxiety association, outpatients with new diagnoses of panic disorder and/or agoraphobia were examined, as well as non-anxious psychiatric and non-psychiatric outpatients as control groups [33]. Results showed that JHS was present in almost 70% of anxiety cases, versus slightly over 10% of controls. This meant that cases with panic disorders and/or agoraphobia were 17 times more likely to suffer from JHS. Conclusions were valid for women [OR=23.7; CI95% 10.6-52.9] (figure 2), but also for men [OR=10.5; CI95% 3.0-36.3] (figure 3).

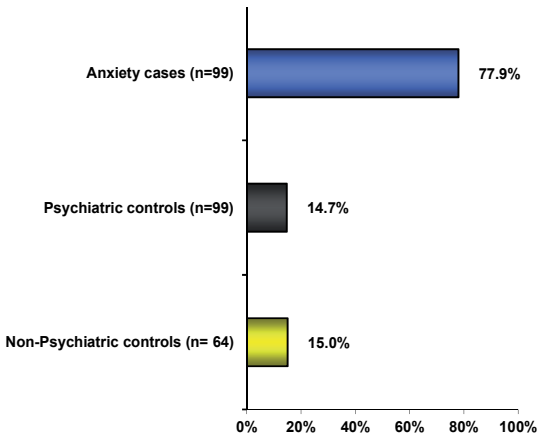

Figure 2. Women frequencies of JHS diagnoses in anxiety cases (n=99), psychiatric (n=99) and non-psychiatric controls (n=64) [33].

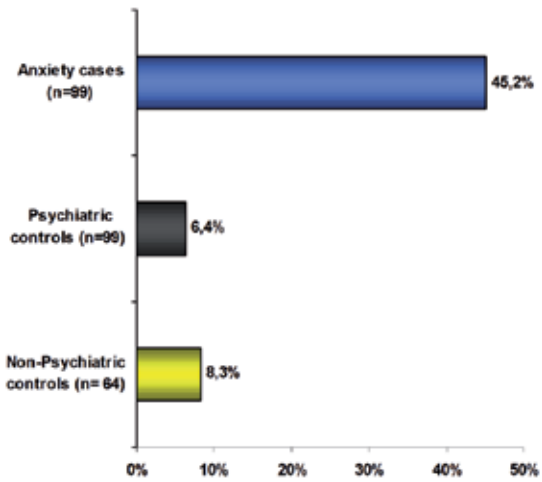

Figure 3. Men frequencies of JHS diagnoses in anxiety cases (n=99), psychiatric (n=99) and non-psychiatric controls (n=64) [33].

Later on, it was suggested that this association needed to be studied in the general population. To that end, a two-phase cross-sectional epidemiological study was carried out in a rural town in order to establish lifetime risk for anxiety and affective disorders in subjects with JHS. A sample of 1,300 individuals were examined at baseline and over 500 were subsequently subjected to follow-up in a two-stage epidemiological study. Hypermobile patients were eight times more likely to suffer from panic disorder (OR 8.2, CI 95% 3.4 to 19.7), eight times more likely to suffer from social phobia (OR 7.8; CI 95% 2.4 to 24.8) and six times more likely to suffer from agoraphobia (OR 5.9; CI 95% 3 to 11.7) than non-JHS patients. Results were valid for both genders. No differences were found for other anxiety disorders or mood disorders [22].

In the same sample of general population it was also reported that hypermobiles had significantly higher scores in fear and phobia scales, reinforcing the hypothesis that intensity of fears is greater in subjects with JHS [34]. We assessed fear intensity and frequency using a modified version of the Fear Survey Schedule (FSS-III). When we compared the groups with and without joint hypermobility, the mean total scores for both genders were significantly higher for the hypermobile group (figure 4). These results showed that the association of JHS and phobic anxiety is sustained for intense fears and might represent a susceptibility factor for these anxiety conditions.

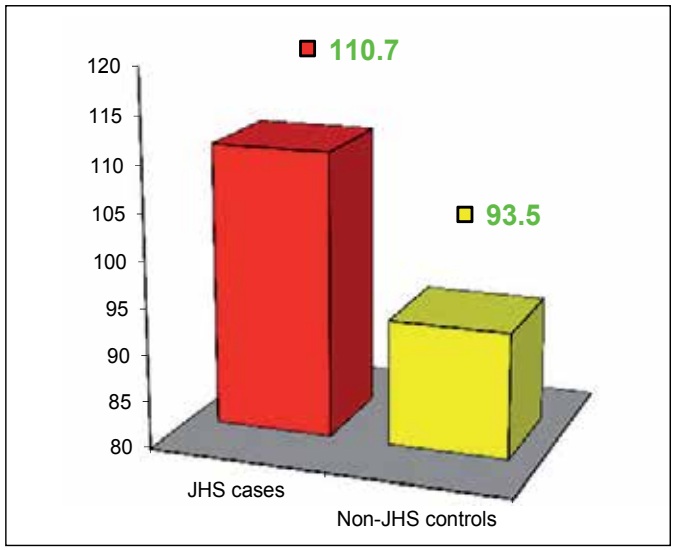

Figure 4. Mean total scores of the Fear Survey Schedule (FSS-III) in JHS cases (n=182) and non-JHS controls (n=1,123) [34].

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The same design was replicated in 2011 in a sample of 150 nonclinical students [35]. Severe fears and daily consumption of cigarettes, alcohol, coffee, and chocolate were compared with the hypermobility scores. We found significant differences when comparing severe fears between the groups with and without hypermobility (7.6 vs. 11; p = 0.001). The frequency of chocolate intake was also significantly higher among subjects with joint hypermobility (31.2% vs. 51.2%; p = 0.038). There were no significant differences regarding cigarette (19.5% vs. 19.3%), alcohol (36.6% vs. 34.9%), and coffee (46.3% vs. 35.8%) consumption. Therefore, these patterns of consumption may be interpreted as self-treatment attempts of subsyndromal anxiety in hypermobile subjects (figure 5).

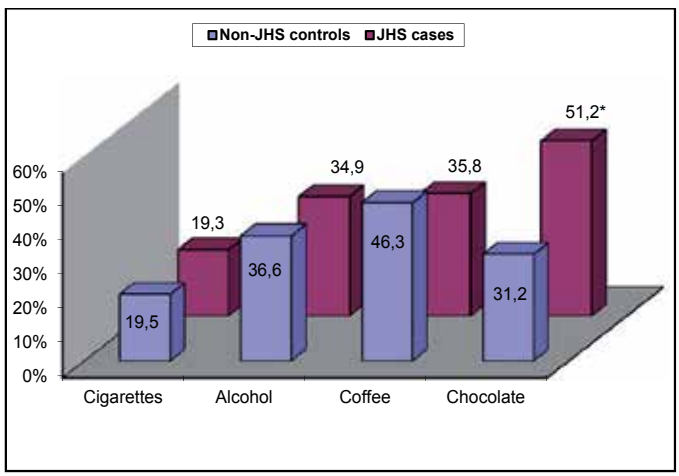

Figure 5. Frequencies of daily consumption of cigarettes, alcohol, coffee, and chocolate in JHS cases (n=41) and non-JHS controls (n=109) [35]. *p = 0.038

In 2004, our group also assessed a non-clinical sample of subjects working in the same company (N=526) [36]. Subjects with JHS had significantly higher scores in STAI trait anxiety [female average: 16.5 vs. 11, p<0.001] [male average: 13 vs. 11, p<0.03]. STAI state anxiety scores were also higher among hypermobile subjects, although not significantly (figure 6).

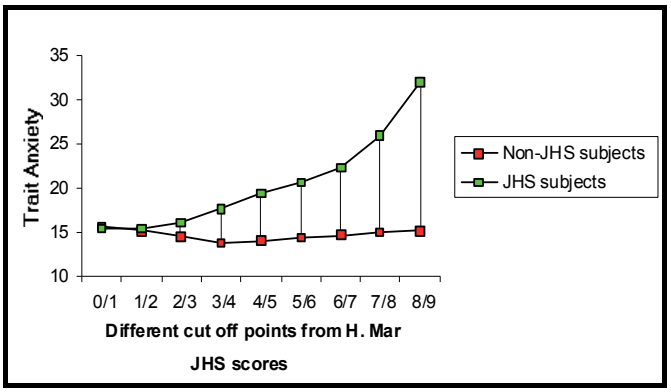

Figure 6. STAI trait anxiety scores (range: 0-60) in 203 women with or without joint hypermobility according to all possible cutoff scores on the Hospital del Mar hypermobility criteria [36].

In 2005, we studied schizophrenic outpatients (N=124) with the hypothesis that anxiety disorders mediated by JHS were not symptoms, but an independent comorbid entity in schizophrenic patients [37,38]. Joint Hypermobility was noticeably more likely among panic disorder/phobia-clustered schizophrenic patients, than among the non-comorbid group (OR = 9.35; IC = 95% [3.85-22.73]; $p<0.0001$). The cluster panic disorder/phobia had higher scores in fear scales and schizophrenia positive symptom scales. We are now performing a voxel-based morphometric study in order to examine brain structure, comparing magnetic resonance images of 20 schizophrenic-anxious patients and 20 schizophrenic patients. The preliminary results indicated gray matter volume differences in the schizophrenic-anxiety group in the dorsolateral prefrontal cortex related to the interaction between both conditions. Our findings suggest that the schizophrenic-anxiety group is characterised by specific neural abnormalities that cannot be explained by the presence of schizophrenia or anxiety, but by their conjunction, and this might result in a certain symptomatology [39].

After several significant cross-sectional studies we sought to conduct a prospective incidence analysis that assesses whether JHS could be a risk factor in developing anxiety conditions [23].

The main objective was to determine the cumulative incidence of anxiety disorders in a cohort of young subjects recruited from the general population who had not developed any type of anxiety condition up to then; consequently we planned a scheduled 15-year follow-up covering subjects from late adolescence to adulthood. The total population sample was 1,305 subjects, and in order to observe the development of anxiety disorders during the 15-

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year study period, only the lower age segment (at that time subjects aged between 16 and 20) included in the town's municipal registry was invited to participate. We sought to describe the occurrence of new cases of anxiety disorders during the study period, therefore the exclusion criterion for the study was having already had an anxiety disorder at baseline examination. At baseline, 158 subjects were screened for participation in the study, and after the 15-year follow-up the final sample comprised 137 subjects (86.7% retention rate). Results showed that cumulative incidence of panic/agoraphobia at follow-up was significantly higher for the JHS group (41.4%) than for the control group (1.9%) with relative risk of 22.3 (CI 95% 4.6-108.7), p<0.0001, (NNT 3, CI 95% 2.9-2.3). Incidence of social phobia and simple phobia was also significantly higher for the JHS group at (RR=6.52; CI 95% 1.7-24.2) p<0.001 and (RR=3.31; CI 95% 1.1-9.6) p=0.02, respectively (table 4). Moreover, anxiolytic drug use was nearly fourfold higher among JHS subjects compared to non-JHS.

Recent work from another Spanish group [40] has shown again a high prevalence of JHS (61.8%) among panic subjects compared with 10.9% in the healthy control group and 9% in the psychiatric control group. Interestingly these authors found an intermediate figure among subjects suffering from fibromyalgia (25.4%). A paper from a Turkish group [41], albeit declaring no significant association, also found JHS in 59.5% of panic disorder patients with mitral valve prolapse, in 42.9% of patients without mitral valve prolapse but also in 52.6% of control subjects. Gülsün et al. [42], studying subjects with thorax deformities, found that the anxiety level of males with thorax deformity and JHS is higher than males with thorax deformity without JHS. And finally, Baeza-Velasco [43] also found high prevalence of social anxiety and joint hypermobility among subjects of high stature.

Total Sample n = 137	**JHS Status**				*RR*	*95% CI*	*P*
	JHS present *n* = 29		JHS absent *n* = 108				
	n	%	*n*	%			
Anxiety Disorders							
Panic/Agoraphobia	12	41.4	2	1.9	22.3	(4.6 to 108.7)	0.0001***
Social Phobia	7	24.1	4	3.7	6.5	(1.7 to 24.2)	0.001*
Simple Phobia	8	27.6	9	8.3	3.3	(1.1 to 9.6)	0.02*
GAD	7	24.1	9	8.3	2.9	(0.97 to 8.62)	0.14 ns
Other Disorders							
Depression/Dysthymia	7	24.1	7	6.48	3.7	(1.2 to 11.7)	0.15 ns

JHS, Joint Hypermobility Syndrome according to Beighton criteria assessed at baseline. GAD, Generalized Anxiety Disorder Statistical significance: * p<0.05, ** p<0.001, *** p<0.0001, ns: non significant

Table 4. Incident cases and relative risk after 15 years of follow-up according to JHS status [23].

	Type	Popul.	N groups	Sex	Age	JHS ass.	Association tendencies
Bulbena et al., 1993 [21]	CC	Spain	114 JHS 59 CTL	Matched	Matched	Beighton	JHS cases: 5 x Aph and 7 x PD
Martin-Santos et al., 1998 [33]	CC	Spain	99 PD &APh 99 Psychiatric CTL 64 Medical CTL	Matched	Matched	Beighton	PD cases: 17 x JHS
Benjamin et al., 2001 [52]	CC	Israel	101 PD 39 Healthy CTL	35 / 65 64 / 36	39.3 (11) 23.4 (3)	Beighton	No statistically significant relationship
Bulbena et al., 2004 [22]	E	Spain	1305 subjects	45.7 / 54.3	43.4 (18.3)	Beighton	JHS cases: 6 x Aph, 8 x SPh and 8 x PD
Gulpek et al., 2004 [41]	CC	Turkey	42 PD & MVP 35 PD 38 MVP CTL	Matched	Matched	Beighton	No statistically significant relationship
Bulbena et al., 2004 [36]	D	Spain	526 subjects	61.4 / 38.6	25.4 (3)	H. Mar	JHS cases: higher scores in STAI trait anxiety
Bulbena et al., 2005 & 2007 [37,38]	D	Spain	124 SCHZ	54 / 46	33.6 (10)	Beighton & H. Mar	Schizophrenic & PD cases: 9 x JHS and higher positive symptoms
Bulbena et al., 2006 [34]	D	Spain	1305 subjects	45.7 / 54.3	43.4 (18.3)	Beighton	JHS cases: higher scores in fear and phobia scales
Gülsün et al., 2007 [42]	CC	Turkey	52 thorax deformity 40 CTL	Males	21.9 (1.3)	Beighton	JHS cases: higher scores in HAM-A
Baeza-Velasco &Bulbena 2009 [43]	D	Several countries	158 high stature	46.8 / 53.2	25.7 (8.1)	Hakim & Grahame	JHS cases: higher scores in LSAS
García-Campayo et al., 2010 [40]	CC	Spain	55 PD 55 Psychiatric CTL 55 Fibromyalgia 55 Healthy CTL	Matched	Matched	Beighton	PD cases: 13 x JHS
Pailhez et al., 2011 [35]	D	Spain	150 subjects	44 / 56	16.4 (0.6)	Hakim & Grahame	JHS cases: higher scores in fear and phobia scales
Bulbena et al., 2011 [23]	C	Spain	137 subjects	53.3 / 46.7	31.9 (2.4)	Beighton & H. Mar	JHS cases: 22 x PD, 6.5 x SPh and 3.3 x Ph

Table 5. Relationship between JHS and anxiety disorders. Basic features of studies reviewed. D, descriptive study; CC, case–control study; C, cohort study; E, epidemiological study; CTL, controls; PD, Panic disorder; Aph, Agoraphobia; MVP, Mitral valve prolapse; SCHZ, Schizophrenia; SPh, Social phobia; Ph, Specific phobia. Sex expressed in percentage (%) male/female. Age expressed in mean (SD).

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5. Weather, medical conditions and panic attacks

The relationship between meteorological variables and human behaviour has been subject of conjecture since Hippocrates. This interaction has been held more in popular belief than in scientific verification. However, since mid 1900s it has been more thoroughly studied, and we are now in a better position to test popular beliefs regarding this connection. Numerous studies in different fields have been carried out in an attempt to assess this relationship and its implications. Studies about meteorological variables and stroke onset [44], myocardial infarction [45] and arthritic pain [46] have shown significant results. Moreover, subjective experience from patients, such as variations in pain thresholds and mood swings when the weather changes, points towards this association and paves the road towards further research.

There are few studies designed to specifically assess the association between meteorological variables and clearly defined psychiatric disorders. Our group has studied this relationship with anxiety disorders [47]. Anxiety disorders are a clinically heterogeneous group that should be evaluated by differentiating panic and non-panic anxiety states due to the different clinical features present in each. Panic disorder has been associated with JHS, which is not seen in generalized anxiety disorder. Due to this association, the physical variables tend to be more relevant. This evidence has partly motivated the need to assess the association of meteorological variables with anxiety disorders and panic attacks separately and specifically.

All psychiatric emergencies attended at a general hospital in Barcelona (Spain) during 2002 with anxiety as main complaint were classified as panic or non-panic anxiety according to strict independent and retrospective criteria. Both groups were assessed and compared with meteorological data (wind speed and direction, daily rainfall, temperature, humidity and solar radiation). Seasons and weekend days were also included as independent variables. Episodes of panic were three times more common with the *poniente* wind (hot wind), twice less often with rainfall, and one and a half times more common in autumn than in other seasons (table 6). These three trends (hot wind, rainfall, and autumn) were accumulative for panic episodes in a logistic regression formula. Significant reduction of episodes on weekends was found only for non-panic episodes. Panic attacks, unlike other anxiety episodes, in a psychiatric emergency department in Barcelona seem to show significant meteorotropism.

	Any Anxiety Days			**Panic Anxiety Days**			**Non-panic Anxiety Days**		
Variables	**OR**	(95%CI)		**OR**	(95%CI)		**OR**	(95%CI)	
Poniente Wind	**1.23**	0.66	2.36	**3.32**	1.76	6.34	**0.60**	0.30	1.15
Saturday-Sunday	**0.69**	0.43	1.09	**0.92**	0.55	1.52	**0.55**	0.34	0.89
Autumn	**1.63**	0.99	2.72	**1.67**	1.00	2.77	**1.40**	0.86	2.27
Rain	**0.78**	0.49	1.26	**0.55**	0.31	0.93	**0.94**	0.58	1.51
Whole Model p	0.11			0.0003			0.035		

Table 6. Odds ratio for days with anxiety (all, panic and non panic), through logistic regression models [47].

On the whole, the results show a higher meteorological sensitivity in patients suffering from panic disorder. In these patients, warm wind increases the risk by three, rain onset reduces it to one-half, and autumn increases it by one and a half. This is not observed in non-panic anxiety, where meteorological effects were not found to be significant.

6. Perspectives

There is enough evidence showing that comorbidity of anxiety disorders and some medical conditions share a similar physiopathological mechanism mediated by the clinical features of JHS. Having arrived at this point, it might be relevant to remind the high association of JHS and the so called dysautonomia. In this way, significant research by Gazit and colleagues [48] found that symptoms related to anxiety such as palpitations, light-headedness, nausea, shortness of breath, hyperventilation, tremulousness, chest discomfort, fatigue, etc., were significantly more common among patients with JHS. Moreover, they found that orthostatic hypotension, postural orthostatic tachycardia syndrome and uncategorized orthostatic intolerance were present in 78% of the studied patients with JHS compared to 10% of control subjects. Thus, they suggested that dysautonomia could be an extra-articular related feature of JHS. It is plausible that the autonomic nervous system of patients with JHS might be overeactive to some environmental stimuli like the weather.

However, under the "modern" name dysautonomia not only anxiety features can be found [49] but also many symptoms described for more than two centuries in the present group of anxiety disorders [50]. Anxiety manifestations are among the most difficult to identify in the clinical practice even in patients suffering from generalized anxiety disorder, in which only 13% present anxiety as main complaint. Although dysautonomia and anxiety disorders are not in the same spectrum, they probably overlap.

In this sense, Eccles et al. have studied associations between regional cerebral grey matter and hypermobility in healthy volunteers. They found that bilateral amygdala volume distinguished those with hypermobility from those without it. Their data implicate the amygdala as a likely neural substrate mediating previously reported clinical associations between hypermobility, anxiety and psychosomatic conditions. Anxiety is linked theoretically to the abnormal generation and mapping of bodily arousal through the engagement of amygdala and insula. Enhanced interoceptive sensitivity also points to a more finely tuned sensory representation of internal bodily signals within the hypermobile group. Finally, they suggest that hypermobility is a multisystem phenotype that could mediate clinical vulnerability to neuropsychiatric symptoms [51]. Therefore, the link between JHS and dysautonomia provides an interesting physiological connection to interpret this unexpected association between a "somatic" and a "psychiatric" condition.

Our results address the biological basis of anxiety and a common source of this condition with other constitutional disturbances in relation to connective tissue and the autonomic nervous system. Patients with a diagnosis of JHS provide a highly valuable opportunity for an in-depth study of the genetic basis of anxiety. Anxiety is also a co-

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morbidity and a risk factor in itself for a poor prognosis in several psychiatric diseases, as is the case with schizophrenia and bipolar disorders. These diseases also provide opportunities to further explore the connection between joint hypermobility and the development of anxiety in these conditions.

It is also important to point out a possible application of this evidence; as patients with JHS are at greater risk of suffering from anxiety conditions, it would be desirable to prevent the development of anxiety disorders by means of community programs at the very early stages of development. We strongly recommend screening for joint hypermobility in routine health assessment protocols in teenagers and early adulthood subjects. Even though the clinical evaluation of JHS is not extremely difficult, it does inevitably require formal training and an external validation of the procedure. In this context, some anamnestic questions might be useful for detecting positive cases at risk of suffering from anxiety disorders.

7. Conclusions

Finally, several conclusions can be made after more than 30 years of active research and clinical work in that field.

First, the association between anxiety (clinical and non clinical) and JHS is strong and replicated in several setting and samples.

Second, both conditions carry high genetic and heritable load. This is clinically very well established, but at the genetic level, there is no clear conclusion yet. Our finding of an interstitial duplication of human chromosome 15 (named DUP 25) as responsible for this association (with a non-Mendelian mechanism of disease-causing mutation) is now actively revisited.

Third, according to the type and number of somatic conditions found in the otherwise named "endogenous" anxiety disorders (panic, agoraphobia and social phobia), it seems that these patients tend to suffer from a particular cluster of disorders, particularly, osteomuscular, irritable bowel, hypo/hyperthiroid, migraine, asthma, etc. It might well be that all these conditions share some common abnormalities in the autonomic nervous system as well as in the collagen structure as found in JHS. This may be a diathesis not yet identified, but worthy to investigate.

And fourth, the autonomic disregulation, although very difficult to assess at that level, may be one of the clues to understand the association, and also to develop appropriate treatments.

In summary, this intriguing relationship gives rise to several physio-pathological questions and prevention-related issues. JHS is a risk factor for anxiety disorders, worthy of evidence-based identification in the context of preventive psychiatry not only among adults but also among at-risk pediatric populations.

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Chapter 10

Anxiety Syndromes and Their Correlates in Children and Adolescents: A Two-Year- Follow-Up Study at Primary Health Care in Mexico City

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Additional information is available at the end of the chapter

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1. Introduction

Anxiety disorders are among psychiatric conditions the earliest to manifest, with a median age at onset of 15 years, using retrospective information (WHO ICPE, 2000). As a group, anxiety disorders are frequent and persistent in childhood and adolescence. The prevalence of anxiety disorders in nonrefered children 4-6 years old has been estimated in 6.1% (Briggs-Gowan et al., 2000), and studies on older children and adolescents have reported lifetime prevalence ranging from 8.3% to 27.0% (Costello et al., 2005). Separation anxiety disorder (SA), specific phobias (SP) and generalized anxiety disorder (GA) are the most common. Left untreated, anxiety disorders tend to have a chronic and unremitting course (Yonkers et al., 2003; Ramsawh et al, 2009) and also increase the risk for adult psychiatric disorders (Pine et al., 1998; Costello et al., 2011).

In primary care settings studies have shown that approximately 9% to 15% (Benjamin et al., 1990; Costello, 1989) of 7- to 11-year-olds meet the criteria for an anxiety disorder, and at least 17% in pediatric patients (Chavira et al., 2004). Most contact with GPs is for physical health problems; only 2–5% of child and adolescent consultations involve presentations with emotional or behavioural problems (Giel et al., 1981). Pediatric anxiety disorders often feature somatic complaints such as abdominal pain, chest pain or discomfort, headaches, nausea, or vomiting, and are often comorbid with medical conditions such as asthma and other atopic disorders (Ramsawh et al., 2010). However, children and adolescents with mood and anxiety disorders in primary care and pediatric settings are underrecognized, not commonly

treated onsite, and less likely than youths with behavioral disorders to be referred to specialized mental health settings (Wren et al., 2003, 2005).

Mental health presentations may also relate to educational or social issues and other risk factors for functioning and development rather than to diagnosable disorders per se. In children, anxiety disorders can be associated with school absenteeism or school refusal, poor academic performance, or grades that are lower than would be expected based on the child's abilities (Mazzone et al, 2007). It is the concerns of parents that typically alert the primary care clinician to psychosocial issues (Dulcan et al., 1990), but parents are often either unaware of their child's internalizing symptoms or do not see a need for services (Wu et al., 1999; Caraveo et al., 2002).

2. Mental health surveillance for children and adolescents: A pilot study at a primary care center in Mexico City

2.1. Background

Having identified that children's and adolescent's mental health problems are frequent and unrecognized conditions in Mexico City (Caraveo et al, 2002) and that an epidemiological study on the general population showed evidence about the familial risk for developing psychopathology acoss three generations (Caraveo et. al., 2005), a pilot study aimed on the surveillance of children's and adolescent's mental health at primary care level was launched. The initiative was conceived as a potential action-research oriented project for the enhancement of the role of primary care in the preventive actions that are needed for mental health care. Primary care has great potential as a source of education, triage, and frontline intervention. However, this role requires simple and efficient methods and tools to accurately identify, in collaboration with the family, the child's core areas of difficulty (Wren et al., 2005).

Eventually, the information to be gathered by this program may contribute to a better understanding of the natural history of different psychiatric syndromes and disorders such as attention deficit and hyperactivity disorder, affective disorders, anxiety disorders and other neuro-psychiatric conditions. All of these produce varying degrees of handicap and may create a risk for other disorders such as alcohol and drug abuse (Merikangas et al., 1998; Hofstra et al. 2000), hence the importance of their surveillance, early detection and care.

As a first step in the development of this pilot study, the concurrent validity and efficiency of the Brief Screening and Diagnostic Questionnaire (CBTD for its initials in Spanish) was evaluated. The CBTD was built based on our previous experience using the Report Questionnaire for Children, RQC (Caraveo et al., 1995) adding 17 items to explore symptoms frequently reported as motives for seeking attention at the out-patient mental health services. The aim was to include cardinal symptoms that could lead to identify probable specific syndromes and disorders, based on the parent's report. The instrument was tested and further developed using information gathered from a general population sample. Internal consis-

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tency showed a Cronbach's alpha of 0.81 with a 0.75-0.85 range by age groups; cluster and factor analyses identified eight groups of symptoms that correlate with the most frequent syndromes seen in children and adolescents (Caraveo, 2006). Logistic regression analyses were then performed between cardinal symptoms for different diagnoses and the rest of the items from the questionnaire, and statistically significant associations were evaluated clinically and compared to psychiatric syndromes as defined by the DSM-IV (APA,1994) and the ICD-10 (WHO, 1993) classifications. Based on these results, algorithms for probable psychiatric syndromes, including subclinical forms, were created (Caraveo, 2007a) and the concurrent validity between some of them and the psychiatric diagnoses of children who received care at two out-patient mental health services showed a fair agreement (Yule's Y: 0.43- 0.55; Caraveo, 2007b). However, as psychiatric diagnoses did not follow a structured clinical interview, there was the need to confirm these results using a standardized evaluation and on primary health attendants in order to evaluate the screening instrument adequacy for establishing a surveillance of mental health in childhood and adolescence.

Results showed an overall Sensitivity of 68%, Specificity of 82%, Positive Predictive Value (PPV) of 88% and a Negative Predictive Value (NPV) of 57%. When two or more CBTD syndromes are present the PPV is almost 100%. Concurrent validity showed a fair agreement for most of the CBTD syndromes as compared to DSM-IV diagnoses (Caraveo et al., 2011).

Once established the validity and efficiency of CBTD as the basic tool for screening purposes, an impairment measurement was considered as a priority for the surveillance pilot study, along with the obtention of psychiatric antecedents in both parents. Also, as besides genetic predisposition a variety of mechanisms have been postulated as being responsible for intergenerational continuity of psychopathology such as impairments in parenting and dysfunctional family relationships (Malcarne et al., 2010), and because along the field work of the surveillance study, these issues were frequently reported by the population, they were subsequently assessed during the two-year follow-up.

As this chapter is focused on anxiety disorders in clildren and adolescents, we will review research on these aspects as related to anxious children and adolescents.

2.1.1. Familial antecedents

Findings from family studies, either using a "top-down" design where the children of parents with anxiety disorders are evaluated or a "bottom-up" design which ascertain the parents of children with anxiety disorders, have clearly establish the cross-generation transmission of anxiety from parents to children (Klein & Pine, 2002). A detailed revision of the literature has been presented in a previous work (Caraveo-Anduaga, 2011).

An epidemiological study on the general population of Mexico City investigated the presencce of psychopathology across three generations (Caraveo et al., 2005). Anxiety syndromes, as defined in the Brief Screening and Diagnostic Questionnaire (CBTD) showed a familial transmission pathway that is consistent with results from studies on Caucasian populations in developed countries (Klein & Pine, 2002), suggesting that familial risk for devel-

oping anxiety disorders is a fact, thus not limited by ethnicity or culture, but mediated by socio-economic conditions (Caraveo-Anduaga, 2011).

Results showed that comorbid anxiety disorders in grandparents seem to interact with anxiety-only as well as with anxiety comorbid disorders in parents, determining a robust morbid risk for the generalized anxiety screening syndrome in descendants, while the familial anxiety risk across generations for the anxiety with inhibition syndrome is less pronounced.

Results considering only the adult proband's information showed that parent's history of anxiety-only as well as comorbid anxiety-depression were significantly associated with both screening anxiety syndromes in their offspring. Male children developed more generalized anxiety as compared to females, and the relationship with spouse was inversely associated with the presence of the syndrome of anxiety with inhibition in the descendant. Additionally, household higher income showed a significant association with the presence of the generalized anxiety syndrome in the children, and poor adult proband's own health perception was associated with both anxiety syndromes in their offspring (Caraveo-Anduaga, 2011).

A limitation of the study was that as the principal objective of the survey was focused on adult population, only one adult was selected at each household, and so familial risk across generations, was based on information about only one parent.

2.1.2. Functional impairment

Functional impairment describes the impact of psychopathology on the life of the child with respect to daily life activities (Üstun & Chatterji, 1997); it refers to ways in which symptoms interfere with and reduce adequate performance of important and desired aspects of the child's life (Rapee et al., 2012). Most common conceptualisations indicate three areas of impairment within family, school and social domains. Ezpeleta et al. (2001) identified three dimensions: interference with parents, peers and education.

Different authors have shown the importance of including impairment indicators in the diagnostic definitions in order to reduce the prevalence rates of the disorders in epidemiological studies (Bird et al., 1988; Roberts, et al., 1997; Shaffer, et al, 1996; Simonoff et al., 1997). The knowledge of the degree of impairment is also necessary for the proper identification of those persons affected by a psychological disorder or in need of psychological help.

Measures of functional impairment besides being an aid in case definitions in epidemiological studies and in nosology are useful for studies of treatment effectiveness, planning services, service eligibility determination, evaluating and planning of programs, but, mainly, they are used as outcome indicators (Ezpeleta et al., 2006).

Available instruments of level of functioning could be classified either as one-dimensional or multidimensional. For the definition of impairment three primary measurement strategies have been identified (Bird et al., 2000): a) measures that incorporate the symptoms and their correlates into the definition of disorder, b) specific impairment measures associated with each diagnosis, and c) global omnibus impairment measures.

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Goals for assessment of functional impairment should help to decide what the best strategy is. If the goal is to decide if a child needs intervention or not, a global strategy could be used, but if the objective is to plan the areas of intervention, then a decomposed instrument could be more appropriate.

Anxiety disorders are especially susceptible to impairment thresholds; however, the importance of impairment is uncertain in early diagnoses. Moreover, anxiety symptoms that are not impairing in early childhood may become so as development and life-experiences continues (Malcarne et al., 2010). Thus, knowledge of the degree of impairment is a necessary component for the surveillance of anxiety and other children's mental health disorders at the primary care level.

Kashani & Orvaschel (1990) in a community sample of 210 children and adolescents found that children diagnosed with anxiety disorder demonstrated greater impairment on both the physical and cognitive measures on self-competence, temperamental flexibility, and levels of self-esteem than non-clinic controls. Research on the psychosocial implications of anxiety indicates the disabling consequences affecting schooling and academic functioning, peer relationships, autonomous activities, self-esteem, family functioning and overall psychosocial impairment (Strauss et al, 1988; Bell-Dolan & Brazeal, 1993; Kendall et al., 1992; Wittchen, Nelson & Lachner, 1998; Essau et al., 2000).

Manassis and Hood (1998) determined the correlates of anxiety disorders that were predictive of impairment. They concluded that predictors were different depending on disorder. The impairment for generalized anxiety disorder was mainly determined by psychosocial adversity, but in the case of phobia, it was determined by mothers' ratings of conduct problems of the child, the depressive symptoms reported by the child, the maternal phobic anxiety, and the development difficulties suffered by the child.

Whiteside (2009) found that the greatest impairment report from both the child and parents was associated with obssessive compulsive disorder and social anxiety disorder, followed by separation anxiety disorder, and then generalized anxiety disorder. Thus, level of impairment seems to be associated with the type of anxiety disorder. However, literature suggests that there are many shared risk or associated factors for psychiatric morbidity and functional impairment in children (Wille N, et al, 2008).

2.1.3. Child-rearing and parenting practices

Darling and Steinberg (1993) defined child-rearing style as 'a constellation of attitudes toward the child that are communicated to the child and create an emotional climate in which the parent's behaviours are expressed'; it describes the quality of the parent-child relationship, whereas parenting practices describes the content and frequency of specific parenting behaviour (Stevenson-Hinde, 1998).

In the literature on child-rearing style, the term 'care' is interchangeably used with warmth, acceptance, nurturance, affection, responsiveness or supportiveness on the one end of the dimension and rejection, hostility or criticism on the other.

Ever since the seminal paper of Bell and Chapman (1986) about the child's influence on parental behaviour, parenting is no longer considered to be a purely parental characteristic affecting the child, but rather an interactional phenomenon in which parent and child participate and reciprocally influence one another.

Relationship may be reciprocal, that is, anxious child influences the parental style exhibited and vice versa (Samerof & Emde, 1989; Thomasgard & Metz, 1993; Bögels and Brechman-Toussaint, 2006).

Behavioural genetic research (Rowe & Plomin, 1981; Plomin & Daniels, 1987) has shown that environmental factors that all children in a family share may have a different influence than those that are unique. Child-rearing style is often considered to belong to the shared environment, but when the contribution of the child to parenting style is taken into consideration, it should rather be regarded as part of the nonshared environment. When differences in parenting behaviour regarding different children within the same family are very outspoken, this is called parental differential treatment (Lindhout, 2008).

Anxiety disorders could be conceptualized, considering the multi factorial aetiological view of the phenomenom, as a self-perpetuating cycle of elevated biological responses to stress, debilitated cognition and avoidance of stressful circumstances reinforced by environmental factor including a parenting style, which interferes with children's attempts at solving their own problems, and instead emphasizes threat in situations, and encourages children's avoidance behavior. The exposure to traumatic or aversive situations also increases the risk of children developing anxious responses (Webster, 2002).

Studies have shown that parents of anxious children behave in ways that increase the chance that their child behaves in an anxious manner. High levels of maternal control and anxiety, and maternal rejection and depression (Rapee, 1997) as well as less accepting, aversiveness, intrusiveness, overinvolved, over protective and more controlling parenting styles have been found associated with anxiety disorders in children (Siqueland et al., 1996; Hudson & Rapee, 2001; Wood et al., 2003; Moore et al., 2004; McLeod et al., 2007; Hudson et al., 2008).

2.1.4. Family style of solving problems and domestic violence

Family relationships are viewed as critical factors influencing a child's social and emotional development (Hannan & Luster, 1991; Levitt, 1991). A number of broad classes of dysfunction such as psychosocial stress, poverty, parental marital discord, parental psychopathology, maltreatment, and parental emotional unavailability, have been associated with both internalizing and externalizing problems (Gotlib & Avison, 1993).

Exposure to conflict has been shown to influence children directly. Witnessing adult anger is physiologically and affectively stressful for children, and exposure to conflict has been shown to influence children indirectly through its effect on parenting and parents' psychological wellbeing. Some researchers have shown that the effects of parental conflict can be more harmful to children than parental absence through death or divorce (Emery, 1982; Jekielek, 1998; Mechanic & Hansell, 1989; Peterson & Zill, 1986). Marital fighting has been

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found to be more predictive of children's functioning than divorce (Cummings, 1994; Jekielek, 1998). More specifically, the quality of the marital relationship in early life has been found to predict future anxiety in the child (Bögels & Brechman-Toussaint, 2006).

In children exposed to chronic violence, increasing sensitization has been reported. Hennessy et al. (1994) found that children exposed to violence, in comparison to peers, were more fearful and emotionally reactive to videotaped scenes of anger between adults. Sensitization may be related to hypervigilance, the tendency to anxiously scan the environment for possible threat that is one of the hallmarks of posttraumatic stress.

Also, deficits in emotion regulation have been observed in children exposed to uncontrolled anger and distress in the very figures they would turn to for soothing and solace (Graham-Bermann & Levendosky, 1998).

Exposure to violence at home is recognized as a form of child maltreatment. Witnessing domestic abuse, especially when it is perpetrated against the mother, in itself is a traumatic experience. Although children growing up in violent homes do not consistently show cognitive deficits, they often display academic problems. Distractibility and inattention in school may occur as a result of the trauma that is associated with exposure ot violence. Research suggest that children exposed to domestic violence show a range of emotional and behavioral problems including insecure attachment in younger children and both externalizing and internalizing problems in the school years (Wenar & Kerig, 2006).

Some children experience negative effects in the short term, others have both short and longer term effects, and still others seem to experience no effects related to witnessing violence. Children's age and sex, as well as severity, intensity and chronicity of the violence are variables that play a role in the outcome of the exposure. In a longitudinal study of a sample of 155 children followed from birth through adolescence, Yates et al. (2003) found that exposure to violence in the home was an independent predictor of externalizing problems in boys and internalizing problems in girls. A study in Canada reported that children aged 4 to 7 years old who witnessed violence at home showed more overt aggression two and four years later. For boys the experience was also linked to indirect aggression, and for girls, with anxiety (Moss, 2003).

2.2. Objective

This chapter will focus on testing whether the basic issues included for the surveillance of mental health in childhood and adolescence are somehow significantly associated with the presence of anxiety syndromes in children an adolescents attended at a primary care setting and followed along a two-year period.

The specific goals for this report are:

1. Confirm familial associations between parental psychiatric history and anxiety CBTD screening syndromes in their offspring.
2. Determine if a higher score on the scale for the assessment of impairment is associated with anxiety CBTD screening syndromes in children and adolescents.

3. Determine if a higher score on the scales examining child-rearing and parental practices are associated with anxiety CBTD screening syndromes in children and adolescents.

4. Determine if a higher score on the scale for the assessment of a potential dysfunctional environment at home is associated with anxiety CBTD screening syndromes in children and adolescents.

5. Evaluate the morbid risk of these variables for the development of anxiety CBTD screening syndromes.

2.3. Method

All consecutive children and adolescents aged 4 to 16 years attended during a six-month period at a primary care health center (PCHC) were included for this study. Children and adolescents already in treatment at the mental health service were excluded. Informed consent was obtained from the parents of the minors at the beginning of the study. At the initial interview, socio demographic data was obtained and parents responded the Brief Screening and Diagnostic Questionnaire (CBTD). Whenever a probable case was detected, parents were advised to seek help from the mental health service at the PCHC or at another facility. The cohort was followed for two years (2005-2007); at each consecutive evaluation a follow-up version of the CBTD was used and complementary information was gathered at different points of time as will be explained.

2.3.1. Instruments

1. The Brief Screening and Diagnostic Questionnaire (CBTD for its initials in Spanish) is a 27-item questionnaire answered by the parents of the child exploring symptoms frequently reported as motives for seeking attention at the outpatient mental health services. Presence of the symptom requires that each item has to be reported as "frequently" presented. The internal consistency of the questionnaire showed a Cronbach's alpha of 0.81, range: 0.76 to 0.85 (Caraveo, 2006). Diagnostic algorithms in order to define probable DSM-IV disorders in children were created based on data from the general population epidemiological study (Caraveo, 2007a). The generalized anxiety screening syndrome was defined as follows: Key symptom: a positive response to the question: Does the child gets scared or nervous for no good reason?, and at least two of the following: can´t seat still, irritable, sleep problems, and frequent nightmares. The anxiety with inhibition screening syndrome was defined as follows: Key symptom: a positive response to the question: Is the child excessively dependent or attached to adults?; and at least two positive answers on the following: aloof, frequent headaches, afraid of school, physical complains without a medical problem, sleep problems, low weight, overweight, do not work at school, and backward compared to other children. Concurrent validity of the two screening anxiety syndromes, generalized anxiety and anxiety with inhibition, as compared to DSM-IV anxiety diagnoses using the E-MiniKid standardized interview (Sheehan et al., 1998; 2000) showed Kappa agreement to be 0.53 and 0.68 respectively, and using Yule´s Y coefficient results were 0.65 and 0.92 respectively.

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Receiver Operating Characteristic Curves (ROC) analyses showed Area under the Curve (AUC) to be 0.82 and 0.78 respectively (Caraveo-Anduaga et al., 2011).

2. Psychiatric parental antecedents about anxiety, affective and substance-use disorders were obtained following the Family-history research criteria (Andreasen et al., 1977; 1986; Kendler et al., 1997) as was used in the general population study (Caraveo-Anduaga, 2011).

3. Functional impairment in children and adolescents was measured using the Brief Imparment Scale (BIS) (Bird et al., 2005) which is a 23-item questionnaire that has three sub-scales exploring interpersonal relationships, work/school performance and self-attitudes. Each question is responded in Likert scale with 4 options: 0= never or no problem; 1= some problems; 2= several problems; 3= serious problems. The internal consistency of the BIS in our population showed a Cronbach's alpha of 0.87.

4. The Parent Practices Inventory (PPI) (Bauermeister et al. 1995 as presented in Barkley R., Murphy K. & Bauermeister J., 1998) is a 37-item questionnaire exploring child-rearing as well as disciplinary practices. Two dimensions were identified: a positive one that considers approval, acceptance, positive motivation and affection as predominant practices, while the negative dimension includes inconsistency, cohersion and negative affect. Each question is evaluated in a 4-point Likert scale: 0= never or almost never; 1= rarely; 2= frequently; 3= very frequently. The internal consistency of the PPI in our population showed a Cronbach's alpha of 0.87.

5. The style of solving problems at home was explored with a 7-item scale adapted from answers used by Kessler in the National Comorbity Study. In the present study they were asked as follows: All persons solve their conflicts in different manners. How often do you and your spouse/partner display the following conducts when there is a conlict? Insults or swores; become furious; sulk or refuse to talk; stomp out of the room; say something to spite; threaten to hit; smash or kick something in anger. Each item is responded in a 4-point Likert scale: 0= never; 1= rarely; 2= sometimes; 3= always. The internal consistency of this scale in our population showed a Cronbach's alpha of 0.98. If some kind of physical violence was reported on the previous scale, it was asked if the child have witnessed the episodes.

2.3.2. Procedure

Field work started on May of 2005 and in an intensive way, children and adolescents aged 4 to 16 years attending the general health clinicians at the PHC were assessed. During the vacation period, months of July and August, attendance during the morning turn was numerous but after that, it was parctically reduced to the afternoon turn. Moreover, new elegible subjects became fewer, so that in December it was decided to end the incorporation phase of the study and start preparing the first follow-up evaluation.

Besides the clinical evaluation using the CBTD in a follow-up version, information about familial psychiatric antecedents of both parents, (that was initiated during the last two months of the incorporation phase), as well as the assessment of impairment in the child us-

ing the BIS were sistematically obtained. It is important to note that even tough follow-up evaluations were cost-free and that reminder of appointments were made, the participation of the study population was scarse as shown in Table 1. In order to deal with this, telephone interviews were carried out by the child psychiatrists working in the project under the supervision of the principal researcher (JC).

For the second follow-up, assessments started on July 2007; based on the previous field clinical work, it was decided to incorporate measures of parental child-rearing practices and of domestic violence. Also, besides clinical follow-up appointments at the PHC, and telephone interviews, it was decided to have home-interviews. For this purpose, psychologists with experience in community studies were trained in the use of all the instruments, and a computarized program was created in order to facilitate the assessments, control, and management of the information. This strategy probed to be more efficient as a higher participation of the study population was accomplished; altough losses were considerable as shown in Table 1. At each follow-up interview, we look for that preferably the informant would be the same person as in the initial assessment.

2.3.3. Analyses

Longitudinal morbid risk in terms of the odds ratio was calculated using the random effects logistic regression analysis as our interest was in the individual development over time of dichotomous outcome variables (Twisk, 2003), for this chapter the two screening anxiety syndromes in children and adolescents.

Bivariate analyses between anxiety syndromes and each independent variable were performed. Scores of the different scales used in the study were converted into dummy variables using quartiles, where higher scores indicated major problems.As each independent variable of interest and its corresponding measure was incorporated at different times along the study period, the number of observations are somehow different in each analysis.

Multivariate analysis including all variables was performed in terms of the odds ratio using the random effects logistic regression analysis. It was assumed that child-rearing practices as well as the style of solving problems at home were the same during the two-year period.

2.4. Results

A total cohort of 846 consecutive children and adolescents patients attended at the PHC was initially evaluated. Girls represented 55% and boys 45%, with a mean age of 9 years (s.d. 3.5). On 87% the informant was the child's mother. For 60% of the cohort at least one follow-up was completed, and in 21%two follow-up interviews were done (Table 1).

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Children/ Adolescents	Initial Evaluation		1 year follow-up		2 year follow-up	
N	**%**	**n**	**%**	**n**	**%**	
Interviewed	846	100	298	35.2	454	53.7
Not interviewed	-	-	548	64.8	392	46.3

Table 1. Interviewed population

The total prevalence of the anxiety screening syndromes at the initial interview was 29.4% (95%CI: 26.4, 32.5) for the generalized anxiety syndrome, and 31.2% (95%CI: 26.4, 35.9) for the anxiety with inhibition syndrome. Both anxiety syndromes were slightly more frequently reported in boys than in girls. In adolescents anxiety syndromes were more frequent among girls. Prevalence of both anxiety syndromes tended to be somehow similar to the initial prevalence at the one-year follow-up, but they both considerably dimisnished at the two-year follow-up; prevalence of anxiety with inhibition decreased to be less than a half of the initial prevalence (Table 2).

2.4.1. Is the morbid risk higher for developing anxiety syndromes in the offspring when anxiety parental psychiatric antecedents are present as compared to when they are not?

The analysis of the association between specific types of pychiatric parental antecedents and the two anxiety syndromes in the offspring shows that parental antecedents of anxiety-only, and comorbid anxiety with depression, as well as with substance abuse are significantly associated with both types of anxiety syndromes in the offspring. Parental antecedents of depression are associated with generalized anxiety syndrome in the offspring, but the odds ratio is considerably lower; and parental antecedents of substance abuse alone, are not significantly associated with neither anxiety syndromes in the offspring (Table 3).

2.4.2. Does a higher impairment score is significantly associated with each anxiety syndrome? If so, is it different for each anxiety disorder?

For this analysis, 741 observations were included; 187 correspond to observations on subjects presenting generalized anxiety, 25.5%, and 135 presenting anxiety with inhibition, 18.2%.

For the next tables, on the second column, the proportions of observations with each anxiety syndrome as related to scores on the BIS are presented. The odds ratio in tables represent the longitudinal strenght of the association between those observed subjects with anxiety syndromes within the corresponding quartile of the impairment scale as compared to observed subjects with anxiety syndromes within the first quartile.

Initial assessment	4 – 5	6 – 8	9 – 12	13 – 16	TOTAL (95%CI)
Boys	(n= 88)	(n= 99)	(n= 128)	(n= 66)	(N= 381)
Generalized anxiety	29.5	34.3	36.0	22.7	31.5 (26.8, 36.2)
Anxiety with inhibition	43.2	38.4	28.0	18.2	33.3 (26.0, 40.6)
Girls	(n= 87)	(n= 112)	(n= 157)	(n= 109)	(N= 465)
Generalized anxiety	20.7	29.5	26.7	33.0	27.7 (23.6, 31.8)
Anxiety with inhibition	27.6	39.3	22.9	30.3	29.4 (23.2, 35.7)
1 year follow-up					
Boys	(n= 15)	(n= 30)	(n= 54)	(n= 34)	(N= 133)
Generalized anxiety	53.3	30.0	40.7	17.6	33.8 (25.7, 42.0)
Anxiety with inhibition	40.0	36.7	24.1	11.8	25.6 (18.1, 33.1)
Girls	(n= 18)	(n= 45)	(n= 56)	(n= 46)	(N= 165)
Generalized anxiety	27.8	20.0	30.3	32.6	27.9 (21.0, 34.8)
Anxiety with inhibition	38.9	20.0	25.0	15.2	22.4 (16.0, 28.9)
2 year follow-up					
Boys	(n= 9)	(n= 54)	(n= 51)	(n= 69)	(N= 183)
Generalized anxiety	11.1	22.6	34.7	17.7	23.2 (16.9, 29.4)
Anxiety with inhibition	11.1	28.3	14.3	10.6	16.9 (11.4, 22.5)
Girls	(n= 38)	(n= 60)	(n= 92)	(n= 81)	(N= 271)
Generalized anxiety	0.0	15.5	32.3	21.2	20.7 (15.8, 25.6)
Anxiety with inhibition	0.0	17.2	16.7	11.2	12.8 (8.7, 16.8)

Table 2. Prevalence of anxiety syndromes at the initial assessment and follow-ups

Nearly half of the observations on children and adolescents with any screening anxiety syndrome are reported as having considerable impairment and with strong longitudinal morbid risk in terms of the odds ratio. Another one fith of the observations on children and adolescents with any screening anxiety syndrome shows moderate impairment as well as moderate longitudinal morbid risk. Notably, one quarter of the observations on children and adolescents presenting anxiety with inhibition also shows some impairment with moderate longitudinal morbid risk (Table 4).

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Antecedents	Generalized anxiety OR (95% CI)	P	Anxiety with inhibition OR (95% CI)	P
Anxiety	9.4 (2.8, 31.8)	.000	8.7 (2.3, 33.2)	.001
Depression	3.9 (1.1, 14.2)	.040	2.6 (0.8, 7.9)	.093
Substance abuse	1.0 (0.2, 5.7)	.979	1.9 (0.3, 10.4)	.464
Anxiety depression	6.5 (2.4, 17.8)	.000	4.4 (1.6, 11.9)	.004
Anxiety, depression Substance abuse	21.7 (6.7, 70.6)	.000	5.2 (1.9, 14.5)	.002

No.obs: 1003; No. gps.433; Wald chi2=33.03; gl=5; p= 0.0000;Wald chi2=17.18;gl=5; p= 0.0042

Table 3. Specific parental antecedents and anxiety syndromes in the offspring

BIS total score	Generalized anxiety %	OR (95% CI)	P	Anxiety with inhibition %	OR (95% CI)	P
0-4	13.9	1.0	.	10.4	1.0	
5-8	18.1	2.0 (0.8, 4.9)	.149	25.9	4.7 (1.7, 12.8)	.003
9-12	22.5	5.5 (2.0, 14.6)	.001	17.8	5.0 (1.6, 15.2)	.005
13-48	45.5	19.1 (6.6, 55.1)	.000	45.9	20.6 (6.5, 65.9)	.000

No.obs: 741; No. gps.540; Wald chi2=34.75;gl=3; p= 0.0000;Wald chi2=26.97;gl=3; p= 0.0000

Table 4. BIS impairment total score and anxiety syndromes

Further analyses on the different sub-scales of the BIS show that interpersonal relationships are significantly impaired in all of the observations of anxious children and adolescents as compared to those observed in the first quartil (Table 5).

Interpersonal Sub-scale score	Generalized anxiety %	OR (95% CI)	P	Anxiety with inhibition %	OR (95% CI)	P
0	11.8	1.0		12.6	1.0	
1-2	32.1	4.3 (1.7, 10.7)	.002	37.8	4.5 (1.7, 11.6)	.002
3	12.8	11.7 (3.4, 40.5)	.000	12.6	10.6 (2.7, 41.2)	.001
4-20	43.3	17.2 (6.1, 48.7)	.000	37.0	10.0 (3.3, 30.4)	.000

No.obs: 741; No. gps.540; Wald chi2=31.0;gl=3; p= 0.0000;Wald chi2=18.00;gl=3; p= 0.0004

Table 5. BIS interpersonal relationships sub-scale and anxiety syndromes

Seventy percent of the observations on anxious children and adolescents show moderate to severe impairment on the school/work sub-scale of the BIS as compared to those observed in the first quartile (Table 6).

School/work Sub-scale score	Generalized anxiety %	OR (95% CI)	P	Anxiety with inhibition %	OR (95% CI)	P
0-1	20.3	1.0		17.8	1.0	
2	9.1	0.8 (0.3, 2.3)	.725	10.4	1.0 (0.3, 2.8)	.992
3-5	34.2	3.7 (1.6, 8.4)	.002	34.8	3.4 (1.4, 8.2)	.006
6-21	36.4	14.7 (5.5, 39.4)	.000	37.0	14.7 (4.9, 43.9)	.000

No.obs: 741; No. gps.540; Wald chi2=32.26;gl=3; p= 0.0000;Wald chi2=25.17;gl=3; p= 0.0000

Table 6. BIS work/school performance sub-scale and anxiety syndromes

Finally, on the self attitudes sub-scale, 85% of all the observations on children and adolescents presenting anxiety with inhibition show different degrees of impairment that are significantly diferent from those in the first quartile, as compared to 60% of the observations on children and adolescents with generalized anxiety syndrome (Table 7).

Self-attitudes Sub-scale score	Generalized anxiety %	OR (95% CI)	P	Anxiety with inhibition %	OR (95% CI)	P
0-1	22.5	1.0		14.1	1.0	
2-3	20.3	1.0 (0.4, 2.4)	.978	25.2	3.5 (1.4, 9.2)	.010
4-5	22.5	3.7 (1.3, 10.4)	.012	28.9	7.5 (2.7, 21.1)	.000
6-18	34.7	8.1 (3.0, 22.0)	.000	31.8	8.5 (3.1, 23.6)	.000

No.obs: 741; No. gps.540; Wald chi2=21.31;gl=3; p= 0.0001;Wald chi2=19.77;gl=3; p= 0.0002

Table 7. BIS self-attitudes sub-scale and anxiety syndromes

2.4.3. Does the exposure to a more outrageous family environment is significantly associated with each anxiety syndrome? If so, is it different for each anxiety disorder?

Bivariate analyses between anxiety syndromes and the score on the style of solving problems at home scale (SSPHS) do not show a significant association with either anxiety syndrome in children and adolescents; however, a higher score on the SSPHS was close to be significantly associated with generalized anxiety (Table 8).

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SSPHS score	Generalized anxiety %	OR (95% CI)	P	Anxiety with inhibition %	OR (95% CI)	P
7-8	27.5	1.0		26.4	1.0	
9-11	25.0	1.2 (0.3, 6.1)	.784	24.0	1.2 (0.4, 3.3)	.790
12-15	13.7	0.2 (0.05, 1.2)	.089	16.3	0.7 (0.2, 2.1)	.526
16-28	33.8	3.4 (0.9, 11.9)	.060	33.3	2.3 (0.8, 6.6)	.129

No.obs: 794; No. gps.321; Wald chi2=12.75;gl=3; p= 0.0052;Wald chi2=4.42;gl=3; p= 0.22

Table 8. More outrageous family environment and anxiety syndromes

Having witnessed physical violence at home was found significantly associated with generalized anxiety syndrome in children and adolescents, OR= 2.6. (95% CI: 1.2, 5.9), but not for anxiety with inhibition, OR= 1.3 (95% CI: 0.6, 2.6).

2.4.4. Does the exposure to a parental's less positive reinforcement rearing practice is significantly associated with each anxiety syndrome? If so, is it different for each anxiety disorder?

Bivariate analyses show that a higher score on parental's less positive reinforcement rearing practice is only associated with observations on children and adolescents with generalized anxiety as compared to those in the first quartile (Table 9).

Less positive reinforcement sub-scale score	Generalized anxiety %	OR (95% CI)	P	Anxiety with inhibition %	OR (95% CI)	P
0-17	25.7	1.0		29.1	1.0	
18-23	17.2	0.7 (0.3, 2.0)	.507	21.2	0.7 (0.3, 1.7)	.490
24-28	25.6	2.4 (0.8, 6.7)	.103	17.3	0.7 (0.3, 1.8)	.463
29-51	31.5	2.9 (1.1, 7.9)	.033	32.4	1.6 (0.7, 3.8)	.244

No.obs: 1088; No. gps.444; Wald chi2=9.71;gl=3; p= 0.0212;Wald chi2=4.27;gl=3; p= 0.2336

Table 9. Less positive reinforcement practices and anxiety syndromes

2.4.5. Does the exposure to a parental's more negative reinforcement rearing practice is significantly associated with each anxiety syndrome? If so, is it different for each anxiety disorder?

Bivariate analyses show that exposure to a parental's higher negative reinforcement is significantly associated with roughly one third of the observations on children and adolescents

with either anxiety syndromes. However, the strenght of the association is higher on the offspring with general anxiety (Table 10).

Negative reinforcement Sub-scale score	Generalized anxiety %	OR (95% CI)	P	Anxiety with inhibition %	OR (95% CI)	P
1-5	25.3	1.0		23.5	1.0	
6-8	14.2	0.4 (0.2, 1.2)	.112	18.4	0.9 (0.4, 2.4)	.918
9-12	22.0	1.5 (0.5, 4.3)	.442	24.6	1.8 (0.7, 4.4)	.186
13-37	38.5	5.6 (2.2, 14.3)	.000	33.5	2.8 (1.2, 6.8)	.018

No.obs: 1088; No. gps.444; Wald chi2=25.41;gl=3; p= 0.0000;Wald chi2=7.84;gl=3; p= 0.0494

Table 10. High negative reinforcement practices and anxiety syndromes

Multivariable analysis using the random effects logistic regression shows that for both anxiety syndromes in children and adolescents parental psychiatric antecedents and a higher score on the BIS are the only two predictive variables significantly associated with the outcome. The contribution of parental psychiatric antecedents in terms of the odds ratio is considerably higher for generalized anxiety than for anxiety with inhibition, and impairment is higher in this latter syndrome than in generalized anxiety (Table 11).

	Generalized anxiety	P	Anxiety with inhibition	P
No. of Familial antecedents	4.7 (1.8, 11.9)	.001	1.9 (1.1, 3.4)	.024
Less positive reinforcement	1.3 (0.7, 2.4)	.365	0.7 (0.5, 1.2)	.177
Higher negative reinforcement	1.2 (0.6, 2.2)	.626	1.3 (0.8, 2.2)	.311
Conflict resolution	1.4 (0.8, 2.6)	.248	1.0 (0.6, 1.6)	.980
Witnessed agression	0.6 (0.1, 2.5)	.455	0.8 (0.2, 2.6)	.662
Impairment	1.9 (1.2, 3.3)	.011	2.5 (1.4, 4.2)	.001
Sex female	0.7 (0.2, 3.0)	.684	1.1 (0.4, 3.4)	.835
Age	1.1 (0.9, 1.3)	.264	0.9 (0.8, 1.1)	.315

No.obs: 454; No. gps.:307; Wald chi2=17.90;gl=8; p= 0.0220;Wald chi2=18.32;gl=7; p= 0.0189

Table 11. Predictor variables and anxiety syndromes

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2.5. Discussion

This study has shown that variables included for the surveillance of mental health problems in children and adolescents at a primary care setting, probed to be useful and complementary for the study of anxiety syndromes as defined in the CBTD. Furthermore, results are consistent with findings reported in the literature on child's anxiety disorders as previously reviewed, although none to our knowledge have attempted to collect them as a whole in a primary care setting and evaluate their risk contribution for anxiety disorders in children and adolescents.

Results obtained on the association between specific parental's psychiatric antecedents and the two anxiety syndromes replicated our previous findings in general population (Caraveo-Anduaga,2011) in that anxiety parental's psychiatric antecedents either alone or comorbid with depression and substance abuse are significantly associated with the development of anxiety syndromes in their offspring.

The odds ratios in the present study are higher than most of the crude odds ratios found on the general population study. For example, the strength of the association between parental's antecedents of anxiety-only and general anxiety syndrome in the offspring was OR= 5.7 (95% CI: 2.1, 15.9) in the general population, while in the present study is OR=9.4 (2.8, 31.8). An explanation for such differences is that regression coefficients calculated with logistic GEE analysis, as in the general population study, always will be lower than the coefficients calculated with a logistic random coefficient analysis as in the present study (Twisk, 2003).

One currently key issue is the extent to which diagnostic thresholds defining mental disorders represent unique entities that lead to functional impairment (Rapee et al., 2012). Results showed that, as expected, higher scores on the BIS were significantly associated with CBTD's anxiety screening syndromes. For most observations on children and adolescents with the generalized anxiety syndrome, 68%, significant risk impairment was found, mainly on interpersonal relationships and work/school performance. Also, for 90% of the observations on children and adolescents reporting anxiety with inhibition, significant risk impairment is associated, and for this syndrome mainly on interpersonal relationships and self-attitudes. These findings are consistent with other reports in the literature, as previously reviewed (see 2.1.2) and contribution of this study is to have documented its presence and relevance in a primary care setting.

Moreover, it is important to highlight that in the present study only frequency of each symtom on the CBTD determined its rating for presence and persistance, so that impairment measurement was obtained irrespective of symptoms and syndromes. The significant association between the measurement of functional impairment and the CBTD's screening anxiety syndromes not only enhance the accuracy and usefulness of these later, but also, impairments identified with the BIS, may become targets for specific interventions and eventually used as outcome indicators as signaled by Ezpeleta et al. (2006).

The exposure to a more outrageous family environment as evaluated by the SSPHS was not significantly associated with any anxiety syndrome in the offspring. However, having witnessed aggression at home was found associated only with generalized anxiety in children

and adolescents. As reviewed, exposure to violence has been found as an independent predictor of different problems in boys as compared with girls (Yates et al., 2003; Moss, 2003). Further analysis is needed to bring more light about this issue.

Roughly, one third of the observations on children and adolescents reporting any screening anxiety syndrome have been exposed to more adverse child-rearing and parental practices, as measured by the two sub-sacles of the PPI. A less positive reinforcement rearing practice seems to be a risk only for generalized anxiety syndrome, while higher negative reinforcement is for both anxiety syndromes; however, the strenght of the association in terms of the odds ratio is higher for children and adolescents with generalized anxiety. Thus, generalized anxiety syndrome in children and adolescents is associated with more adverse child-rearing and parental practices than children and adolescents presenting anxiety with inhibition. As disscussed for impairment, results from the PPI sub-scales not only showed differences in their association with the two screening anxiety syndromes, but also the information is important for planning interventions.

Finally, among the variables included in the study, it is important to distinguish nonmodifiable risk factors from those that could be modifiable (Opler et al., 2010). Results evaluating the morbid risk of all independent variables on anxiety showed that familial psychiatric antecedent, mainly anxiety, is the major nonmodifiable risk factor for both anxiety syndromes, although slightly higher for generalized anxiety than for anxiety with inhibition syndrome. Impairment, which is the second mayor contributor, is actually a consequence of the psychopathology, so it seems that once an anxiety syndrome is detected, efforts should be directed toward the other modifiable risk factors such as rearing and parenting practices in order to prevent further impairment; diminishes suffering and modify maladjustment.

3. Conclusion

The present report has confirmed that anxiety disorders in children and adolescents attending a primary care center in Mexico City are frequent, persistent and represent a great part of the unmet treatment needs of children's mental health. In order to tackle this problem and enhace the role of primary care in the preventive actions that are needed, results from this pilot surveillance program on child's mental health have developed and adapted simple and efficient tools that identified child's core areas of difficulty associated with the two screening anxiety syndromes. Future work should be focused on acceptable and relatively simple interventions that, as part of a step-care strategy, could modify risk factors such as rearing and parenting practices, evaluating the impact on impairment measures.

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Chapter 11

Anxiety Disorders in Pregnancy and the Postpartum Period

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Additional information is available at the end of the chapter

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1. Introduction

All new mothers are somewhat anxious. Being a mother is a new role, a new job, with a new person in your life and new responsibilities. Anxiety in response to this situation is very common and somewhat adaptive. However, for several reasons, some mothers have excessive worries and experience a severe (and invalidating) level of anxiety in perinatal period. Important gonadal steroid levels modifications have been reported, with as much as a 100-fold variation in serum estrogen levels and a 1000-fold change in serum progesterone levels during pregnancy. These changes can exacerbate such emotional difficulties. Psychological factors may also have an important role to play in the development of anxiety disorders at this time. Often the expectant mother has concerns over the health of the child, the change in lifestyle likely to occur in her own life after the birth of the child (especially if the first child), her own ability to be a good mother, and finances. There are also instances where the pregnancy is unexpected or unwanted, which may further increase stress and anxiety [1].

The postpartum period too is recognized as a time of vulnerability to affective disorders, particularly postpartum depression. In contrast, the prevalence and clinical presentation of anxiety disorders during pregnancy and the postpartum period have received little research attention [2]. In contrast with common belief that pregnancy is a state of well-being with low rates of mental health issues, pregnancy does not protect at all against anxiety and depression [3].

2. Epidemiology and outcomes

There is now a growing realization that many women suffer from either new onset or exacerbation of existing anxiety disorders during perinatal period [4]. Studies of anxiety in pregnancy women show that a significant portion of them are affected [5]. Heron et al., in a large community sample of pregnant women, found that 21% had clinically significant anxiety symptoms and, of these, 64% continued to have anxiety in postpartum [6]. Other studies have also shown higher prevalence rates of anxiety disorders in the postnatal period compared with the general population: 20.4% had an anxiety disorder (approximately two thirds with comorbid depression) and 37.7% of women with a major depressive episode (MDE) had a comorbid anxiety disorder, with a prevalence rate of CIDI diagnosis of 29.2% [7]; 11.1% screened for PAD and 6.1% for PDD, with comorbidity found in 2.1% [8].

Anxiety and depression often occur together, are often present in pregnancy and persist if not treated [9; 10 among others]. These disorders can have a wide range of effects not only for the mother but on the fetus, the infant, partner and other family members (11-13).

Several prospective studies have shown that a prenatal anxiety disorder is one of the strongest risk factors for developing postnatal depression [4;14].

Common themes of severe anxiety during pregnancy include fear of fetal loss or fetal abnormalities. The terrors of parturition have been greatly reduced by analgesia and obstetric care, but pain and injury are still among the fears expressed by over 50% of women. Fear of delivery is often expressed, and other intense fears include those of hemorrhaging to death, or being torn or mutilated. Some women mentioned complication of parturition including maternal death and many are afraid of being alone during delivery [15].

A variety of poor outcomes are associated with anxiety during pregnancy: pre-eclampsia, increased nausea and vomiting, longer sick leave during pregnancy, increased number of visits to obstetrician, spontaneous preterm labor, preterm delivery, low birth weight, low APGAR scores, breastfeeding difficulties, a more difficult labor and delivery with increase of PTSD symptoms related to birth, admission of infant to neonatal care, elective cesarean section (1; 16-18; 19 and 20 for previous reviews).

3. Clinical aspects

The symptoms of anxiety during pregnancy or postpartum might include:

- constant worry;
- nervousness;
- anxiety;
- fatigue;
- restless legs;

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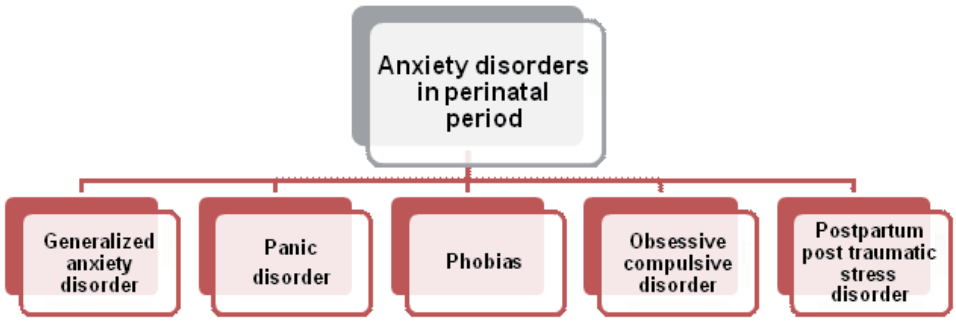
- hypervigilant concerns or attention for the baby;
- extreme lability;
- thoughts of worry regarding the future, or catastrophic events occurring;
- insomnia;
- distractibility and inability to concentrate;
- appetite and sleep disturbance;
- a sense of memory loss;
- physical symptoms like dizziness, hot flashes, vomiting and nausea. [14; 21; 22]

Research shows that there are some risk factors that may predispose some women to anxiety disorders in perinatal period that include:

- family history of anxiety disorders;
- personal history of depression or anxiety
- thyroid imbalance;
- low socioeconomic status;
- unplanned or unwanted pregnancy;
- child care stress;
- personal characteristics like guilt-prone, perfectionistic, feeling unable to achieve, low self-esteem. [23].

Intense postnatal anxiety impairs maternal functioning, causes significant distress and may seriously disturb mother-infant interaction, with consequences raging from maternal neglect and failure to thrive to infanticide [4].

Anxiety disorders can take different forms in perinatal period:



4. Generalized Anxiety Disorder (GAD)

There are few data on the epidemiology of GAD during pregnancy and postnatally. Wenzel et al. found that 4.4% of women in their study met diagnostic criteria for GAD and that over 30% reported subsyndromal symptoms [1, 32].

Sixty-five percent of patients with current GAD report comorbid disorders (most commonly depression, panic disorder, and agoraphobia). GAD, persistent and excessive worry of more than 6 months duration, may be more common in postnatal women than in the general population [23].

Pregnant women with GAD experience excessive worries about a number of life domains along with various physical symptoms such as tension headaches, muscle aches, irritability and poor concentration. Pregnancy itself is associated with role changes, health concerns for the fetus and bodily changes and may form the content of these worries. Diagnosing GAD poses special challenges in pregnancy, since it is normal to have a degree of worry and anxiety in this period of women's life [4].

There are no data on the course of pre-existing GAD in pregnancy. A large-scale community prospective study of around 8,300 women (based on the Avon Longitudinal Study of Parent and Child), which measured anxiety symptoms during pregnancy and postpartum period (from 18 weeks gestation to 8 months postnatally), found while 14.6% scored above threshold at 18 weeks gestation and 8% scored above threshold at 8 weeks postnatally, with 2.4% *de novo* presentation [24].

GAD main symptoms are:

- anxiety;
- apprehensive expectation;
- nervousness;
- fatigue;
- excessive, intrusive and persistent worries;
- a pervasive feeling of apprehension or dread;
- inability to tolerate uncertainty;
- difficulty concentrating or focusing on things;
- muscle tension;
- sleep disturbance;
- feeling edgy, restless, or jumpy;
- stomach problems, nausea, diarrhea.

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5. Panic disorder

Panic disorder is an anxiety disorder characterized by recurring severe panic attacks, for at least one month. A panic attack may be a one-time occurrence, but many people experience repeated episodes.

Due to the physiological changes of pregnancy a woman may be at increased risk of onset or recurrence of panic disorder.

Physiological symptoms such as fear and autonomic arousal symptoms like shortness of breath, pounding heart and dizziness may be misinterpreted in catastrophic ways in relation to the pregnancy [3].

However, recent data suggest that pregnancy may confer some kind of protection against this disturb. In contrast the early postpartum period is reported to be a time of increased vulnerability to panic disorder, with figures ranging from 0.5% to 1.5% at 6 week postpartum [5]. In 1988, Metz and Sichel described panic disorder presenting for the first time in the early postpartum period. They showed that panic disorder affects approximately 10% of postpartum women [cited in 21]. Other important authors described cases of panic disorder presenting for the first time in the postnatal period [4 among others].

Wisner, Peindl and Hanusa, in 1996, found that 11% to 29% percent of women with panic disorder reported an onset during the postpartum period and women with a history of mild panic symptoms have experienced worsening of these symptoms in postpartum period (within the first 2 or 3 weeks and eventually being accompanied by depressive symptoms) [25].

Premenstrual hormonal changes may play a role in panic disorder, which would implicate the role of ovarian hormones in vulnerability to anxiety and panic in the postpartum period [4, 26].

In 1998 Beck conducted a phenomenological study to describe the experiences of the women with panic, in the postpartum period. Through interviews with mothers diagnosed with postpartum panic disorder, the author found six emerging themes describing the essence of the mother's experience:

- theme 1: the terrifying physical and emotional components of panic paralyzed women, leaving them feeling totally out of control;
- theme 2: during panic attacks, women's cognitive functioning abruptly diminished, whereas between these attacks women experienced a more insidious decrease in their cognitive functioning;
- theme 3: during the panic attack, women feverishly struggled to maintain their composure, leading to exhaustion;
- theme 4: because of the terrifying nature of panic, preventing further panic attacks was paramount in the lives of the women;

- theme 5: as a result of recurring panic attacks, negative changes in women's lifestyles ensued lowering their self-esteem and leaving them to bear the burden of disappointing not only themselves but also their families;
- theme 6: mothers were haunted by the prospect that their panic could have residual effect on themselves and their families.

Anticipatory anxiety about future attacks and consequences of these on the fetus can be significantly disabling. The symptoms of panic disorder in perinatal period my worse and some women becoming agoraphobic and socially isolated [23].

Panic disorder main symptoms are:

- shortness of breath or hyperventilation;
- palpitations, pounding heart, or accelerated heart rate;
- trembling or shaking;
- chest pain or discomfort;
- sweating;
- feeling unreal or detached from your surroundings;
- choking feeling
- nausea or abdominal distress;
- feeling dizzy, light-headed, or faint;
- numbness or tingling sensations;
- hot or cold flashes;
- fear of dying, losing control, or going crazy;
- paresthesias (numbness or tingling sensations). [3;4;27].

6. Phobias

"Fear" is the normal response to a genuine danger. Phobia is an irrational fear of an object or a situation leading to avoidance. It is an abnormally fearful response to a danger that is imagined or is irrationally exaggerated. People can develop phobic reactions to animals (e.g., spiders), activities (e.g., flying), or social situations (e.g., eating in public or simply being in a public environment).There is no literature on the exact prevalence and impact of specific phobias such as social phobia or agoraphobia during pregnancy. But there are two specific types of phobia that has been discussed in relation to pregnancy and child birth: tokophobia (intense fear of childbirth) and the phobia for the infant.

Tokophobia can lead to woman avoiding pregnancy, terminating pregnancy of a very much wanted baby or demanding caesarean section in subsequent pregnancies. It has been classified

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as: primary in a nulliparous woman, secondary if the woman has had previous traumatic deliveries or secondary to depressive illness or post-traumatic stress disorder (PTSD) during pregnancy. The prevalence of serious fear of childbirth was 5.5% in women. Is very important to consider factors influencing this fear:

- history of sexual or physical abuse;
- a traumatic gynecological examination;
- previous experience of childbirth and related anxiety;
- myths about labor and childbirth. [3;21]

Fear of childbirth may also be a symptom of PTSD associated with childbirth.

Phobia for the infant: a mother with infant-focused anxiety may develop a phobia for the infant. Brockington [28] describes the fear of cot death and says that a cause of severe chronic anxiety in the puerperium is fear of sudden infant death syndrome. They are mothers who will not let their infants sleep, for fear they stop breathing and other who waken them to see if they are alive. These mothers experience severe insomnia, because of the need to lie awake listening to the baby's breathing; they may check the infant 20-30 times every night.

Symptoms of a phobia include the following:

- feelings of panic, dread, horror, or terror;
- a persistent and overwhelming fear of the object or situation;
- recognition that the fear goes beyond normal boundaries and the actual threat of danger;
- reactions that are automatic and uncontrollable, practically taking over the person's thoughts;
- rapid heartbeat
- shortness of breath;
- trembling;
- an overwhelming desire to flee the situation, all the physical reactions associated with extreme fear;
- extreme measures taken to avoid the feared object or situation [27].

7. Obsessive–Compulsive Disorder (OCD)

Obsessive-compulsive disorder is a relatively common psychiatric disorder with lifetime prevalence rate of 0.8% to 3.2% in the community. It is an important health problem, because it leads to an impairment in the quality of life and functional status and to disabilities in occupational and social areas. Epidemiological studies show that OCD is more frequent in

females compared to males. The mean age of onset of this disorder includes the childbearing years in women. Women with postpartum onset OCD often experience obsessions about harming their baby, they may avoid their infants due to their fear of acting on such thoughts. For this reason, their symptoms often impair their ability to care their infants. This situation may give rise to depressive symptoms [29-30].

The prevalence of OCD during pregnancy has been reported in the range of 0.2% to 5.2% in the literature, the relatively consistent rates among the studies are between 1% to 3%. Obsessive-compulsive symptoms are more frequently seen in pregnant women [29; 31].

The prevalence of OCD in postpartum period has been reported within wide range of 0.7% to 9.0%, and obsessive-compulsive symptoms were described in 14% to 63.5% of postpartum women [15; 32; 33; 34].

There are several case reports showing that pregnancy and postpartum period are associated with the onset of OCD more frequently than other life events [29].

The etiology of postpartum onset OCD is unknown. The acute onset may be due to the dramatic, rapid fall in the female hormones estrogen and progesterone, resulting in a dysregulation of serotonin, which than interacts with any predisposition to mental disorder. Another hypothesis regarding etiology, may be the rapid increase in oxytocin to a high level near the end of pregnancy and during postpartum, which may trigger an exacerbation or the onset of OCD [4].

In literature there are few studies analyzing risk factors for pregnancy induced OCD.

The main risk factors associated with pregnancy onset OCD are:

- primiparity;
- second or third trimester of gestation;
- number of gestations and live birth;
- miscarriage;
- gestational complication;
- positive family history of OCD. [29].

Compared to pregnancy onset OCD, the studies described above illustrate with more details the factors associated with postpartum onset OCD.

The main risk factors associated with pregnancy onset OCD are:

- primiparity (6.57% vs 1.81% multiparous ones);
- the first 4 weeks of postnatal period;
- higher levels of anxiety;
- obsessive-compulsive personality disorder;
- avoidant personality disorder;

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- personal history of major depression;
- the existence of OCD related dysfunctional belief. [29-30].

Symptoms of perinatal OCD can include:

- obsessions, also called intrusive thoughts, which are persistent, repetitive thoughts or mental images related to the baby;
- compulsions, where the woman may do certain things over and over again to reduce her fears and obsessions;
- fear of being left alone with the infant;
- hypervigilance in protecting the infant;
- loss of appetite;
- tremendous guilt and shame;
- horrified by these things. [21; see also www.ppmdsupport.com]

Obsessions are defined as:

1. recurrent and persistent thoughts, impulses, or images that are experienced at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress;
2. the thoughts, impulses, or images are not simply excessive worries about real-life problems;
3. the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action;
4. the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion) [27].

Compulsions are defined as:

1. repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly;
2. the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive [27].

Compared with non-postpartum onset OCD, aggressive obsessions exhibit a tendency to be seen more frequently seen in postpartum onset OCD, and the most common obsessions were contamination and aggressive obsessions. Many authors noted that the aggressive obsessions had 9 times more chances of occurring in a postpartum woman with OCD than in a healthy postpartum woman. The aggressive obsessions mostly include fear of harming the baby [29,

33]. In some instances, sufferers report obsessions having to do with accidental harm, while in others the obsessions involve unwanted thoughts or ideas of intentionally harming the newborn. Some examples of the kinds of postpartum obsessions are as follows:

- the idea that the baby could die while sleeping (S.I.D.S);
- the thought of dropping the baby from a high place;
- the thought of putting the baby in the microwave;
- an image of the baby dead;
- thoughts of the baby choking and not being able to save him;
- unwanted impulses to shake the baby to see what would happen;
- thoughts of yelling at the baby;
- thoughts of poking the baby in the soft spot in her head (fontanel);
- thought of stabbing the baby;
- thoughts of drowning the baby during a bath. [29; 33 see also www.ocfoundation.org/EO_Postpartum.aspx;].

Other women have contamination obsessions that are often focused on the baby:

- microorganisms;
- chemicals or dirt contaminations via her hand or the baby's bottles or foods. [30].

Compared with obsessions, the studies has less frequently focused on compulsive symptoms after the childbirth.

The most common compulsions are:

- cleaning/washing;
- checking.

Some compulsions were related to the baby:

- avoiding kitchen knives;
- not bathing the infant;
- staying physically isolated from the baby;
- checking the breathing or baby's body;
- excessive or ritualized washing or cleaning. [29; 33].

The important thing is that women with postpartum onset OCD, compared to psychotic women, have relatively good insight, do not exhibit psychotic features, don't want to harm the baby, recognize that thoughts/images are unhealthy and take step to protect the baby [32-34].

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Less attention has been focused on the clinical characteristics of OCD in pregnancy [35]. Few reports suggest that contamination obsessions and cleaning/washing compulsions may be seen more frequently compared to other symptoms. Moreover, symmetry obsessions and checking compulsions are frequently observed in pregnant women. Aggressive and contamination obsessions in some pregnant women may be related to the fetus and some pregnant women experience thoughts of harming their unborn child. Often OCD is comorbid with other psychiatric disorders, in particular with major depression. Comorbid depression developed simultaneously or within 2 to 3 weeks after the onset of OCD. There are no studies that reported literature examining comorbid disorders in pregnant women with OCD [29; 34].

When undiagnosed and untreated, postpartum OCD can cause extreme distress in the mother and can also influence the type of care an infant receives, family relationships and interactions [30; 4].

These women run the risk of maternal-infant attachment difficulties [21].

8. Postpartum Post–Traumatic Stress Disorder (PTSD)

The term post-traumatic stress disorder (PTSD) refers to a disorder that can occur following the experience or witnessing of life-threatening events. We usually recognize events like terrorist incidents, serious accidents, or violent personal assaults as being capable of causing such trauma, so, it has proved difficult for people to understand that a "natural" process like childbirth can also be traumatizing. The fact is that a traumatic event can actually be any experience which involves the threat of death or serious injury to an individual or another person close to them (e.g. their baby). A person must then respond with intense fear, helplessness or horror for a diagnosis of PTSD to be made. The reported prevalence of diagnosed PTSD caused by childbirth ranges from 2-3% to 25% in the postpartum women [23].

Research into this field is limited and, to date, it has largely focused on the importance of the type of delivery a woman has undergone. However, recent studies have begun to look at the significance of women's perceptions of their birth experience. Then, it is now generally accepted that PTSD can be a consequence of a traumatic birth experience and important studies demonstrate that women did in fact suffer this type of traumatic stress after birth (see for more infos at www.birthtraumaassociation.org.uk). This type of PTSD are called postpartum post-traumatic stress disorder (PP PTSD) or post natal PTSD (PN PTSD) or "birth trauma".

Most often, this illness is caused by a real or perceived trauma during delivery or postpartum. These traumas could include:

- prolapsed cord;
- unplanned Caesarian section;
- cardiac arrest;

- postpartum hemorrhage;
- induction;
- use of vacuum extractor or forceps to deliver the baby;
- rapid delivery;
- severe toxemia;
- manual removal of placenta;
- premature birth;
- separation from infant in NICU;
- feelings of powerlessness, poor communication and/or lack of support and reassurance during the delivery. [26; 36; see also www.ppmdsupport.com].

Most significant risk factors for postpartum PTSD are therefore the following:

- domestic violence;
- history of sex trauma (e.g. sexual abuse, rape);
- previous adverse reproductive events (e.g. ectopic pregnancy, miscarriage, stillbirth);
- history of mental health problem;
- migration;
- mode of delivery;
- fear for their own safety or that of their child;
- lack of control;
- the attitudes of staff;
- inadequate pain relief;
- poor social support;
- previous traumatic events. [3,5,21, 27; 36; 37 see also www.birthtraumaassociation.org.uk].

A person who has been diagnosed with PTSD will find their normal life interrupted in many ways by a strong and powerful set of emotions and feelings over which they have no control.

Symptoms may start soon after childbirth or they could be delayed for months, and may persist for a long time and resulting in other problems such as depression [see for more infos at www.ppmsupport.com].

General symptoms of postpartum PTSD might include:

- anxiety and panic attack;
- intrusive re-experiencing of a past traumatic event;

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- recurrent intrusive memories;
- flashbacks or nightmares;
- avoidance of stimuli associated with the event, including thoughts, feelings, people, places and details of the event;
- persistent increased arousal (irritability, outbursts of anger, difficulty sleeping an concentrating, hypervigilance, exaggerated startle response);
- reduced consciences status;
- feeling a sense of unreality and detachment;
- depressive symptoms;
- fear of sexual intimacy;
- restricted range of affect;
- sense of a foreshortened future. [21,23; 35 see also www.ppmsupport.com and www.birthtraumaassociation.org.uk].

It is important to understand that, following a traumatic event, sufferers of PTSD are left with a world view which has been altered profoundly and which often leaves them deeply afraid and anxious. The world is no longer considered to be a safe place and it can be difficult to trust the very individuals (health care professionals) who are supposed to be there to help. For those who develop PTSD, the future may look bleak as they struggle to liberate themselves from the images of the trauma they have endured. This can be particularly hard for women with 'birth trauma' because they often suffer these problems at a time when everyone expects them to be happy and positive. As a result, they often end up feeling guilty and this lowers self-esteem [36; 37; see for more info at www.ppmsupport.com].

If untreated, PTSD is associated with increased physical morbidity, subsequent psychiatric illness, accidental and non-accidental death. It may also have the following consequence:

- depression;
- suicide risk;
- an increased incidence of alcohol and other substance abuse;
- profound problems for a woman's relationship with her baby, problems with breast feeding and bonding;
- sexual avoidance;
- tokophobia (fear of childbirth);
- requests for otherwise unnecessary elective caesarean sections in subsequent pregnancies;
- over-vigilance and anxiety about a child's health;
- the impact on a woman's family

- avoidance of future medical care. [4; 36 see also www.ppmsupport.com].

9. Pharmacological and non-pharmacological treatments

Hereafter a short summary of the most commonly proposed treatment of anxiety in pregnancy and postpartum period, bearing in mind that pharmacological approaches, especially in pregnancy but also in breastfeeding period, are to be used with caution, collaborating with gynecologists, and weighting risks and benefits with greater attention than in "normal" patients; and bearing in mind, too, that until now there is a lack of evidence for the effectiveness of psychological therapies for anxiety disorder during the perinatal period (even if it is reasonable to consider that anxiety in pregnancy and postpartum differs little from the same disorders among non-pregnant women in both their presentation and course, and reasonably in the efficacy of its treatment).

Bear also in mind that there are some concerns about diagnostic criteria of anxiety disorders (and of depression, too) in pregnancy, as outlined in Matthey and Ross-Hamid [34] and McGuiness and al. [35], and these might be limitations in the correct use of medications in this period.

Psychological treatments

A detailed description of all the psychotherapies available for treating anxiety is beyond the scope of this chapter [see 24 and 36 for further details], anyway the most recent evidences are very well described elsewhere in this book . It is however useful to remind that cognitive-behavioral therapies are, at now, the golden standard based on efficacy and efficiency results compared to other form of psychological interventions. These therapies can be tailored on the client with more adequacy than other more structured (and ideologically based) form of psychotherapies, and can be of adequately short duration and time-sparing (in front of the time-consuming "job" of being mother, a short and time-sparing approach is desirable). Relaxation techniques are a specific application of CBT, are specifically symptom oriented, and can be proposed as the sole intervention for mild form of anxiety. CBT and relaxation can be exerted in groups, favouring indirect group support.

Interpersonal psychotherapy has gained a growing success, but its efficacy in anxiety problems is still questionable, lacking clinical evidence of efficacy, whereas its efficacy in depression is confirmed.

Psychodynamic psychotherapies, too, have questionable efficacy on anxious problems and require more commitment and time (and money too).

Pharmacological treatments

This section will describe the most frequently used pharmacological treatments to counteract anxiety and the most widely accepted evidences with regard to safety in pregnancy and post partum period.

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Benzodiazepines

Earlier studies suggesting an increase in orofacial cleft defects following in utero exposure to benzodiazepines are counteracted by a recent large prospective study founding no significant association with such (or other) birth defects, although benzodiazepines are associated with negative obstetric outcomes like poor Apgar score at birth, tendency to preterm birth and low birth weight [38].

Nevertheless, benzodiazepines use in pregnancy has still contrasting evidences about safety for the newborn, due to methodological limits in the studies (not consideration of the consequences of maternal illness on fetus, familiar history of malformations, and so on) [39-40], even if the more recent data, considering a more wide spectrum of variables and a better quality in the design of the studies, seem to uphold the global safety of these molecules [41-42] except for anal atresia associated with lorazepam use in the I trimester [40] and for low weight at birth and preterm birth [43].

Regarding to the use of benzodiazepines in the III trimester of pregnancy and peripartum period, a floppy infant syndrome has been described, and also a transient slowing of growth (a complete normalization is however reached in the first year of life) [39,44].

There are some evidences pointing out the at now not yet clear balance risks / benefits of the use of benzodiazepines in pregnancy, especially with alprazolam [45].

According to available studies [45 amongst all], some indications on the use of benzodiazepines during pregnancy are the following:

- 'short-acting' benzodiazepines should be preferred and then can be used safely during pregnancy and breastfeeding if they are only used for a short period (less than 4 weeks)
- use the lowest dose, shorter treatment period, more fractioned dose (to avoid plasma peaks) as possible
- avoid multiprescriptions
- the use of 'long-acting' benzodiazepines should be avoided, in order to avoid accumulation reaction.
- use only benzodiazepines with safety records of long period

Antidepressants

There is a growing number of large prospective studies on **SSRI** in pregnancy and postnatal period, most of the evidence going against an association between any particular selective serotonin reuptake inhibitor (SSRI) and birth defects [48-53]. However some data evidenced an association between SSRI use and negative obstetric outcome like mild degrees of preterm birth and low birth weight [47; 54-56], and there are adverse neonatal outcomes reports including mild degrees of poor neonatal adaptation (neonatal withdrawal syndrome) following SSRI exposure [47,54,56-57], all of them transient. Fluoxetine is associated with a slight increase of negative obstetric outcomes but not of malformations after I trimester exposition [57], the study being supported by Lilly.

An increase of spontaneous abortions has been reported in some studies, even if not statistically significant [59-61].

In particular, these problems are evident using paroxetine. As for benzodiazepine studies, however, these studies suffer of methodological limitations [62-65] and sampling problems [63-64, 66-68,69-70].

Citalopram and escitalopram are associated with a slight increase of spontaneous abortions, comparable with any other antidepressant, and not significant low weight at birth but no increase of malformations [60, 70].

A link between neonatal persistent pulmonary hypertension and late exposure to SSRIs has initially been suggested [71-74] but not confirmed in following studies [75-78], even if some doubts already emerged [79]. An association between paroxetine exposure (especially in the I trimester) and infant cardiovascular malformations has recently been reported [50; 68, 80-83], even if a recent meta-analysis [84] and a large cohort study [85] found no significant association. Despite these results, and having other more "sure" SSRI, it is better and precautionary not to prescribe paroxetine as first line treatment.

There is limited evidence on the use of **SNRIs**, with most available evidence concerning venlafaxine, showing a lack of significative association with an increased risk of major birth defects [46, 50, 59], but a mild association with 'neonatal withdrawal syndrome' [85], neonatal seizures [86] and low weight at birth [87], and transient (resolving in less than 1 week) behavioral signs, but there was also an increase of use of tobacco and alcohol in treated women [88].

Mirtazapine has associated with an increase of spontaneous abortions but not with any increase of malformations [89]. The same results are for **bupropione** [90], **nefazodone** and **trazodone** [91]

Side effects of in utero exposure to **TCAs** are similar to those of SSRIs (i.e. premature delivery, low birth weight, neonatal distress, respiratory problems, hypoglycemia, cyanosis, jitteriness, convulsions, decreased Apgar score and the need for special-care nurseries) but have been reported to be more severe [80-81, 92].

Duration of treatments with antidepressants is not associated with teratogenic risk [93], as well as with gestation period of exposition [94].

Antipsychotics

In relation to antipsychotics, to be avoided as first line treatment of anxiety but useful in certain resistant subtypes of GAD, there are sparse evidence of non significant association with any birth defect, both for first generation antipsychotics [95-96] and for new generation antipsychotics [97-98]. First- and second-generation antipsychotics however have been associated with obesity in pregnancy [97] and high or low birth weight [98-99].

Postpartum and breastfeeding

In relation to breastfeeding, current evidences suggest that SSRIs [51, 100-102] and benzodiazepines with short half-lives [102] are transferred in only low concentrations to breast

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milk. During lactation, benzodiazepine use is not associated with adverse events in newborns [102]. Regarding the use of benzodiazepines during breastfeeding, the little informations available derive from a low number of studies, but the data are converging to a relative safety in their use, even if their use needs some cautions since neonatal metabolism and global clearance is very slow, and benzodiazepines in the long term tend to accumulate [103-104].

A recent review on antidepressants use during breastfeeding period showed an acceptable safety using SSRI and nortryptiline, a cautious use of fluoxetine, and suggesting doxepine and nefazodone to be avoided [105], even if a recent review on antidepressants and breastfeeding suggests as first choice, due to their low degree of excretion into human milk, sertraline, paroxetine and fluvoxamine, not recommending (for their long half life) citalopram escitalopram and fluoxetine [103]. For a complete review about limits and methodological problems in available studies on breastfeeding and use of psychiatric drugs see in particular Llewellin and Stowe [106], Fortinguerra et al. [103] and Moretti [104].

Final considerations about psychopharmacological treatments

As previously described, therefore, there are some (even if acceptable) risks associated with the use of psychotropic medications in this delicate period, but the clinician – GP, psychiatrist, gynecologist (and the mother, and her relatives) have to bear in mind that it should not be assumed that it is always better to avoid medication. Untreated mental health disorders in this period, as seen before, can significantly (and sometimes dramatically) affect the physical and/or mental wellbeing of the woman, the fetus/infant, and significant other(s) and family [24,107-109] (see Table 2 for a summary). So, a careful evaluation of risks (comprehending the naturalistic prevalence and incidence of birth defects - the background risk of birth defects in the general population is between 2% and 4% - compared to the, often low, increase linked to treatments) and benefits has to be carried on, in order to reach a real informed consent of the woman and her significant others to an adequate pharmacological treatment of the most invalidating form of anxiety disorders.

When prescribing a medication for a woman with a mental health disorder who is planning a pregnancy, pregnant or breastfeeding, the following recommendations, even if not new (2007) have to be followed [24]:

- choose medications with lower risk profiles for the mother and the fetus or infant;
- start low and increase slow to the lowest effective dose for the shortest time needed for treatment;
- monotherapy better than combination treatment;
- consider additional precautions for preterm, low birth weight or sick infants
- adequate monitoring of relapse, and discontinuation/withdrawal symptoms

TREATMENT	IN PREGNANCY AND IN POSTPARTUM PERIOD
NON-PHARMACOLOGICAL TREATMENTS	a. Psychoeducational interventions b. Psychotherapy • Cognitive-behavioral therapy (CBT) • Interpersonal therapy (IPT) • Psychodynamic therapy • Mother-infant psychotherapy c. Psychological support d. Progressive muscle relaxation
PHARMACOLOGICAL TREATMENTS	a. Anxyolitics b. Antidepressant c. Antipsychotics
COMBINED TREATMENT	An integrated approach where pharmacological treatment and psychotherapy work together is the best therapeutic intervention to achieve the most successful recovery from symptoms

(from: Beyondblue, 2011) [36].

Table 1.

Fetal/obstetrical outcomes	• Preterm delivery, prolongation of gestation • Lower birth weight, fetal distress • Spontaneous abortion higher risk • Pre-eclampia higher risk • Labour complications
Neonatal outcomes	• Neonatal maladaptation • Higher risk of admission in neonatal ICU • Lower Apgar • Growth retardation, slowed mental development • Behavioral disturbances
Child development	• Maternal-fetal / maternal-infant bonding disturbances • Affect disregulations (tantrums) • Alterations in the development of cognitive, relational, behavioral domains • Higher risk of separation anxiety and disorganized attachment styles • Higher impulsivity and lower QI at 14-15 yrs
Risk to mother	• Poor nutrition and impaired self care • Non compliance to medical advices • Worsening of comorbid medical illnesses • Increased use of substances (tobacco, alcool, drugs) • Postpartum psychiatric complications • Impact of family members

Table 2. Untreated anxiety and aoutcomes (adapted from 107-109)

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Chapter 12

Understanding and Treating Anxiety Disorders in Presence of Personality Disorder Diagnosis

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Additional information is available at the end of the chapter

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1. Introduction

The prevalence of personality disorders varies between 0.5% and 2.5% in the general population and it increases drastically in the clinical population [1, 2]. In a psychiatric population, about one half of all patients have pathological personality [3]. Following the multiaxial classification of the Diagnostic Manual of the American Psychiatric Association (DSM-IV-TR; [1]), Axis II personality disorders are defined as being stable, inflexible, and pervasive patterns of psychological experiences and behaviors that differ prominently from cultural expectations, and that lead to clinically significant distress or impairment in important areas of functioning. In the DSM-IV-TR, there are 10 distinct personality disorders organized into three clusters. Cluster "A" includes three personality disorders considered as odd or eccentric: paranoid, schizoid and schizotypal. Antisocial, borderline, narcissistic and histrionic personality disorders are grouped under Cluster "B", which is considered as the dramatic, emotional or erratic cluster. Finally, Cluster "C" comprises three anxious or fearful personality disorders: the avoidant personality disorder, the dependent personality disorder and the obsessive-compulsive personality disorder. In the next version of the DSM (DSM-V), the task force is proposing some major changes for Axis II and as per the may 1st 2012 online revision[4], the DSM-V will retain six personality disorder types : schizotypal, antisocial, borderline, narcissistic, avoidant and obsessive-compulsive.

The comorbidity between Axis I and Axis II disorders is much documented, and there are some voices in the scientific community that would even question whether or not the distinction between those two axis should be revisited [5-8]. Specifically, Axis II disorders have been found to be strongly associated with anxiety disorders [9, 10] and an increased prevalence of personality disorders has been found in patients with anxiety disorders [11, 12]. Per-

sonality disorders are associated to high social cost and mortality, such as crime, disability, underachievement, underemployment, increased need for medical care, institutionalization, suicide attempts, self-injurious behavior, family disruption, child abuse and neglect, poverty, and homelessness [12]. This underlies the importance of finding optimal treatment for this population, and understanding the mechanisms by which personality pathology interferes with other psychiatric disorders, such as anxiety disorders.

This chapter presents a comprehensive review of the literature on the co-occurrence of personality and anxiety disorders, and the treatment of the latter when comorbidity occurs. First, the influence of personality pathology on anxiety disorders in general is discussed, with no regard to specific anxiety disorders. Afterwards, the clinical features of each of the major anxiety disorders that are comorbid with personality disorders are examined separately. The influence of personality disorders on anxiety disorder symptomatology and on the course of illness is also discussed in terms of treatment. Emphasis will be on the outcome of cognitive and/or behavioral therapy, since its efficacy has been repeatedly established in the treatment of anxiety disorders. The influence of Axis II diagnosis on the outcome of pharmacological treatment of anxiety disorders is also briefly discussed. Major characteristics of the studies that are reviewed in the present chapter are presented in a table. Finally, future research questions on comorbidity of anxiety disorders in the presence of personality disorders are proposed.

2. Co-occurrence of personality disorders and anxiety disorders

From 36% to 76% of patients with anxiety disorders have been found to have a comorbid personality disorder diagnosis, with avoidant, dependent, obsessive-compulsive and paranoid being the most frequent [12]. Thus, anxiety disorders seem to be particularly associated with Cluster C personality disorders [13]. Personality disorders are known to be strongly associated with functional impairment [14], more severe psychopathology, and a decreased response to treatment [15]. When they coexist with anxiety disorders, the latter are characterized by chronicity and more functional impairment that when compared to anxiety disorders without Axis II comorbidity [11]. For example, in a study by Klass and colleagues [16], anxiety patients with comorbid personality disorders were three to four times more likely to have current dysthymia. Furthermore, patients with a personality disorder diagnosis were significantly more likely to present a past major depressive episode, and they received lower scores for current level of functioning, compared with a control group matched on primary anxiety diagnosis, sex, and age [16]. Moreover, the co-occurrence of personality disorders and anxiety disorders has been found to be associated with suicide. In one study, individuals with an anxiety disorder and antisocial personality disorder had more suicidal ideation and suicide attempts, in comparison to individuals with either disorder alone [17]. Finally, personality disorders were reported to have a negative prognostic impact on the naturalistic course of anxiety disorders. Ansell and colleagues [18] found that groups with higher rates of personality disorders generally showed a more complex and variable course of illness, which was characterized by frequent remissions and relapses, and the occurrence of new onsets of anxiety disorders over a 7-year period. Although, their sample was recruit-

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ed among a treatment-seeking population, the purpose of this study was to investigate the naturalistic course of anxiety disorders. Thus, the treatment received was not controlled, and it was not considered in the analysis.

2.1. Etiology of comorbidity

It is likely that multiple mechanisms contribute to the co-occurrence of anxiety and personality disorders. One possible explanation is that Axis I and II disorders are etiologically independent and that apparent high rates of co-occurrence are simply due to high rates of each disorder[19]. However, Ruegg and Frances [12] argued that the high rates of co-occurrence found in several studies are due to sampling bias, since most studies have been made among treatment seeking populations. Given that treatment seeking generally correlates with higher symptomatology severity and with the presence of multiple comorbid disorders, it is likely that these samples overestimate the relationship between anxiety and personality disorders [12]. High rates of co-occurrence have also been explained by issues in assessing personality disorders among individuals with anxiety disorders. This refers to the "state versus trait" issue in comorbidity research [20]. Because mood state tend to color the perceptions, going through an episode of anxiety disorder may affect the patients' perception of their personality, which would result in a distorted report of the latter [19]. Thus, the presence of an Axis I disorder may result in a false positive diagnosis of personality disorder [12], which would lead to an overestimation of the prevalence of personality disorders among individuals with anxiety disorders. Several models have been proposed to explain the high rates of coexisting personality and anxiety disorders, and these are described in the following section.

First, it has been suggested that individuals with personality disorders are more *vulnerable* to develop comorbid disorders. Vulnerability models assume that the disorders are distinct but are causally related, such that the presence of one disorder increases the risk to develop the other [19]. For example, because of their interpersonal difficulties, individuals with personality disorders would be more prone to experience repeated, chronic and acute negative life events, such as failures and losses, which would then increase the risk to develop and/or maintain anxiety disorders [19]. Second, some studies have supported the hypothesis that personality disorder traits are risk factors for anxiety disorders. For example, schizotypal, antisocial, borderline, histrionic and dependent personality traits present in adolescence and early adulthood have been associated with higher risk of having an anxiety disorder by middle adulthood [21]. In one study [22], high narcissistic personality traits, measured one week after trauma, have been associated with an increased risk of developing posttraumatic stress disorder (PTSD) one month and four months after trauma, even when controlling for baseline anxiety disorders. However, Brandes and Bienvenu [23] mentioned that these findings do not consider possible causal mechanisms involved. For instance, personality disorder traits and anxiety disorders could share a common etiology, and personality disorder traits would only be earlier manifestations of these common causal influences [23]. Third, another model of comorbidity refers to overlapping criteria [24] and shared etiology [23]. Thus, characteristics of each disorder are viewed as manifestations of a common dimension of psychopathology, which would suggest that these disorders are not entirely distinct [19]. If they do share etio-

logical factors, a shared genetic influence could be expected. Indeed, some results have supported the hypothesis of a common genetic base to anxiety and personality disorders. For instance, avoidant and dependent personality traits have been found to be more common in first-degree relatives of patients with panic disorder (PD) compared with relatives of control participants [25]. In another study, obsessive-compulsive traits were higher in first-degree relatives of patients with obsessive-compulsive disorder (OCD), compared with relatives of controls [26]. However, these findings could also be explained by environmental influences [23], since patients and their relatives could have lived in a similar environment. Fourth, the pathoplasty conceptualization emphasizes the influence of one condition on the presentation or course of the other, but does not assume a shared etiology [19]. Thus, one condition may have an additive effect on the other condition, or exacerbate the latter [27]. For example, avoidant personality disorder (AVPD) and panic disorder with agoraphobia (PDA) may have a pathoplastic relationship such that the presence of personality traits and anxious predispositions interact to promote the development of personality or anxiety disorders [18]. Finally, it has been suggested that personality disorder traits could be shaped by the experience of having an anxiety disorder in childhood or adolescence [23]. For example, current anxiety disorders among adolescents have been found to predict schizotypal, schizoid, borderline, avoidant, and dependent personality traits in early adulthood, even when controlling for other Axis I disorders during adolescence [28]. However, in this study, personality disorder traits have not been assessed during adolescence, so it cannot be concluded that they were subsequent to the development of anxiety disorders [23]. Results from Kasen and colleagues [29] gave additional support to this model. Indeed, the presence of an anxiety disorder in adolescence was found to predict an increased likelihood of having a paranoid personality disorder in young adulthood, when controlling for personality disorders in adolescence. Also, adolescents who reported anxiety symptoms that were increasing over time were more likely to have a paranoid personality disorder, or an OCPD in young adulthood [29]. The authors suggested that behaviors and thoughts associated with perfectionism and rigidity, which characterized OCPD, may develop to help control anxiety symptoms [29]. Yet, these findings still do not exclude the possibility that personality and anxiety disorders share a common etiology, although in this case, personality disorders would be the later manifestations [23]. Though all these models give interesting explanations to comorbidity of anxiety and personality disorders, they are not mutually exclusive and it is likely that more complex bio-psycho-social models are needed to explain the co-occurrence of these psychopathologies.

3. Influence of personality disorders on the outcome of treatment for anxiety disorders

Since patients with multiple psychopathologies are often excluded from treatment trials, comorbidity is often disregarded [30]. Thus, few controlled prospective studies have specifically examined the effect of comorbid personality disorders on the outcome of cognitive and behavioral treatment (CBT) for anxiety disorders. However, some studies have investigated this area of research, with interesting results.

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The Reich and Green [31] review, based on studies of depressive and anxiety disorders, concluded that the presence of a personality disorder had a negative influence on the outcome of treatment for Axis I disorders. In fact, personality pathology was found to predict a negative outcome of treatment in practically all studies [31]. Another review [20], which covered empirical studies published between 1991 and 1993, yielded similar conclusions. However, with regard to anxiety disorders, only studies that investigated the outcome of treatment for PD or OCD were included in the two previous reviews. Although Reich confirmed the general conclusion that dysfunctional personality traits have a negative effect on the outcome of treatment for Axis I disorders in his latest review [32], he also reported that individuals with comorbid personality disorders show improvement of their anxiety disorder symptoms when treated for their anxiety disorder. However, in the Dreessen and Arntz [33] selective review, personality disorders were not found to predict negatively the outcome of psychological treatment for anxiety disorders. It was concluded that no specific personality disorder was consistently found to affect negatively treatment outcome of anxiety disorders, and that patients with a comorbid personality disorder were not more likely to select themselves out of treatment [33]. Finally, the authors reported that patients with a personality disorder generally do not respond less to cognitive and/or behavioral treatment for their anxiety disorder, compared to patients without a personality disorder. However, these authors also report in their review that personality disorders are found to have a negative effect on the outcome of pharmacological treatment for anxiety disorders.

4. Panic disorder with and without agoraphobia (PD/A)

Among panic patients, prevalence rates of comorbid personality disorders (mostly in the Cluster C) range from 37% to 60% [3, 34-42]. No study has yet established a clear link between a specific type of personality disorder and the diagnosis of PDA [43]. Some have reported a strong association of panic disorder with AVPD [35, 38], whereas others have found higher rates of obsessive-compulsive personality disorder (OCPD; [36, 44]). This being said, Mavissakalian, Hamann, and Jones [45] reported that personality disorders cannot be presumed to have specific etiological significance for PD, given that the personality disorder traits that are generally identified in PD patients are also present, and they are even more pronounced, in OCD patients.

4.1. Initial symptomatology and course of illness

Individuals with comorbid PD and personality disorders tend to present a higher clinical severity [3, 38, 44, 46] and a more chronic course of illness [41] than PD patients without a personality disorder. For instance, the presence of borderline personality disorder (BPD; [18]) or OCPD [47] was found to predict new onsets of PD, when no treatment is considered. In a study by Ozkan and Altindag [3], patients with comorbid PD and personality disorders had more severe anxiety, depression, and agoraphobic symptoms, onset was at younger age, and they had lower levels of functioning. On the other hand, Mellman and colleagues [37] found no significant differences in baseline clinical ratings, and on most measures of chronicity, se-

verity and duration of PD in the presence of a personality disorder. In Ansell et al. study [18], the presence of an AVPD at baseline was even associated with a decreased likelihood of relapsing in their PDA.

In addition, comorbid personality disorders in PD patients have been associated with an increased risk of suicidal thoughts [44, 48] and suicide attempts [48]. In one study [49], all PD patients who had made serious suicide attempts had a comorbid personality disorder. A significant correlation between suicide attempts and comorbid Cluster B personality disorders was reported, particularly with BPD and histrionic personality disorder [49]. Other studies found a similar association of BPD with suicidal ideation [50] or suicide attempts [3] among PD patients. Also, paranoid personality disorder has been reported to predict suicide attempts, and AVPD to predict suicidal ideation among this population [3]. Moreover, it appears that personality disorder criteria do not necessarily need to be met to aggravate the severity of PD. Indeed, studies have found personality disorder traits to be associated with more baseline clinical disturbance among this population. For instance, PD patients with a greater number of personality disorder traits have been found to be more symptomatic on almost all measures of psychopathology [51].

4.2. Influence of personality pathology on the outcome of cognitive and/or behavioral treatment for panic disorder with and without agoraphobia

Studies examining the effect of personality disorders on the outcome of cognitive and/or behavioral therapy for PD have obtained conflicting results. However, as can be expected, many studies have found a negative impact of personality disorders on the outcome of treatment. Tyrer and colleagues [52] randomly assigned 181 patients with generalized anxiety disorder (GAD), PD, or dysthymia to three modalities of treatment: pharmacological treatment, cognitive therapy, or self–help. Their results indicated that the presence of a personality disorder did negatively influence the outcome of cognitive therapy and self–help at the 2-year follow-up test. Using the same sample to measure the effect of time on treatment outcome, Seivewright, Tyrer, and Johnson [53] found that the presence of a personality disorder was still associated with a negative prognostic indicator five years after cognitive therapy. Other studies also found a negative influence of personality disorders on the outcome of CBT [38] or behavioral treatment [54] for PD. Keijsers, Schaap, and Hoogduin [55] found that higher personality psychopathology, as measured by the revised version of the personality diagnostic questionnaire ((PDQ-R; [56]) scores, was related to higher levels of agoraphobic avoidance and higher frequency of panic attacks after behavioral treatment. Yet, the relationship was no longer significant after statistical adjustment for multiple tests [55]. Chambless and colleagues [57] examined the effects of secondary major depression, dysthymia, GAD, and AVPD on the outcome of a behavioral treatment, which mostly consisted of an exposure-based individual treatment, and a group psychotherapy that focused on interpersonal and intrapsychic problems that were believed to maintain their PDA. Their results indicated that AVPD predicted less improvement in the frequency of panic attacks at the 6-month follow-up. Finally, the influence of specific clusters of personality disorders on treatment outcome has been found to vary depending on whether personality pathology was assessed dimensionally or categorically. For exam-

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ple, the presence of a Cluster A diagnosis was the strongest predictor of CBT outcome when assessed categorically, whereas these Cluster A disorders were not associated with CBT outcome when assessed dimensionally [38].

In other studies, comorbid personality disorders have been found to have little or no impact on the outcome of cognitive and/or behavioral treatment for PD. Dreessen, Arntz, Luttels, and Sallaerts [58] results suggest that PD patients with and without personality disorders profit equally from CBT for their PD, although certain personality disorder traits were found to have some impact on treatment outcome. Indeed, OCPD traits were negatively related to treatment outcome, and borderline traits predicted better outcome, but this latter finding was only observed at the 6-month follow-up test. However, given that personality disorders were lumped together to obtain adequate sample sizes, the influence of individual personality disorders on the outcome of CBT for PD was not measured [58]. Black and colleagues [59] studied treatment response in 66 PD patients who had completed three weeks of treatment with cognitive therapy, pharmacotherapy, or placebo pharmacotherapy. Surprisingly, this study yielded different conclusions depending on the measurement method used to assess personality functioning. The presence of a personality disorder assessed by the Structured Interview for DSM-III-R Personality disorders (SIDP; Stangl et al., 1987] was not a predictor of treatment outcome at week four whereas the presence of a personality disorder assessed by a self-report questionnaire was a negative predictor of outcome in the groups receiving cognitive therapy or placebo [59]. In their selective review, Dreessen and Arntz [33] also examined the two previous studies, and the Chambless et al. [57] study. They concluded that personality disorders do not seem to significantly affect the outcome of cognitive and/or behavioral treatment for PD, but when personality disorders are examined separately, AVPD appears to be associated with a less favorable outcome in the long term, although it has no effect on immediate outcome [33]. To our knowledge, two other studies also concluded that patients with and without personality disorders seem to profit equally from CBT for their PDA [60, 61]. Hofmann and colleagues [62] found similar results. Indeed, personality disorder characteristics, as measured by the Wisconsin Personality Disorders Inventory (WISPI; [63]) were not found to predict outcome of CBT for PD. Finally, Kampman, Keijsers, Hoogduin, and Hendriks [64] examined whether Cluster C personality disorders predicted treatment response in a sample of 161 PD patients treated with CBT. Their results indicated that the presence of Cluster C personality disorders did not affect treatment outcome. These researchers [64] suggested that their results may be explained by the use of a self-report questionnaire to assess personality (PDQ-R), which is known to have high sensitivity, and moderate specificity [65].

4.3. Pharmacological treatment

The presence of a comorbid personality disorder has been found to be one of the most robust predictors of nonresponse to pharmacological treatment for PD [66]. For example, Marchesi and colleagues [67], in a study with 71 PD patients, found a negative effect of borderline personality traits on the outcome of selective serotonin reuptake inhibitor (SSRI) pharmacological treatment. In their study, Green and Curtis [35] measured the effect of personality disorders on the outcome of a pharmacological treatment (participants were treated

with a tricyclic antidepressant or an anxiolytic) among 25 PD patients. There was a significant relationship between the presence of at least one personality disorder and relapse, and with regard to specific personality disorders, AVPD was associated with an increased likelihood of relapse. Reich [42] found a negative association between the outcome of pharmacological treatment (benzodiazepine molecules) and the presence of borderline, antisocial, histrionic, and narcissistic personality disorders. However, other studies [62, 68] did not find an influence of personality disorders on the outcome of pharmacological treatment for PD. The Tyrer et al. study [52] mentioned previously also found no influence of personality disorders on the outcome of pharmacological treatment for PD, which is inconsistent with conclusions drawn from Dreessen and Arntz review [33]. This is explained by the fact that the Tyrer et al. study [52] has not been reviewed by Dreessen and Arntz [33], given that it did not meet the "best-evidence criteria" needed to be included in the review. Indeed, the authors only reviewed the studies that met the two criteria that they believed would meet the best designed studies, which are a prospective design, and the use of a structured, or semi-structured, interview.

In some studies, treatment consisted of combined CBT and pharmacotherapy. In one study [69], comorbid personality disorders were associated with a delayed response to pharmacotherapy and behavioral treatment for PD, and the association was stronger for AVPD. In another study [70], 60 PD patients were treated with SSRIs and CBT, or with CBT only. Results indicated that treatment for patients without a personality disorder was significantly more effective with regard to general psychopathology, PD symptoms, and depression. However, there were no differences between groups on overall symptoms of anxiety, as measured by Hamilton Anxiety Scale and Beck Anxiety Inventory [70-72].

5. Obsessive-Compulsive Disorder (OCD)

Studies have found prevalence rates of comorbid personality disorders of 49% to 75% in patients with OCD, and personality disorders from Cluster C were found to be the most diagnosed [45, 73-77]. As can be expected, many studies have reported OCPD to be the most diagnosed among clinical samples of OCD patients [26, 73, 75, 78-82], with prevalence rates of 18% to 55% [75, 78, 80]. However, other studies have found much lower rates of OCPD among OCD patients (6% for Baer et al. [83]; 4% for Joffee, Swinson, & Regan [84]; 4% for Steketee [77]).

5.1. Initial symptomatology and course of illness

OCD patients with comorbid personality disorders do not seem to have more severe OCD symptoms compared to those without personality disorders [76, 77, 80]. Cavedini and colleagues [78] found no differences in the severity of OCD symptoms at baseline between OCD patients with and without OCPD. However, studies indicate more depressive and anxious symptoms, and more impairment in functioning before treatment in OCD patients with comorbid Axis II diagnosis [76, 81]. Bejerot and colleagues [73] found similar results. In their

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study, higher scores on all anxiety scales, and more functional impairment were reported for OCD individuals with comorbid personality disorders. In the Fricke et al. [80] study, the presence of a personality disorder was associated with more depressive symptoms and higher levels of functional impairment. In addition, the presence of an OCPD [18, 85] or an AVPD was found to predict new onsets of OCD, and the presence of a BPD diagnosis at baseline was associated with an increased likelihood of relapsing in OCD, when no treatment was considered [18].

5.2. Influence of personality pathology on the outcome of cognitive and/or behavioral treatment for OCD

Baer and Jenike [86] reviewed the presence of comorbid personality disorders in OCD patients and their influence on treatment outcome. They concluded that schizotypal personality disorder was the only one that predicted poorer outcome of treatment (behavioral or pharmacological) for OCD. Although this Axis II disorder is not particularly common among patients with OCD [26], schizotypal personality disorder and traits have been repeatedly related to poor response to behavioral treatment for OCD [87, 88]. Moritz and colleagues [89] suggest that it may be the positive schizotypal symptoms (e.g. unusual perceptual experiences, paranoid ideation, sensory irritation, magical beliefs) that predict poor treatment outcome. Impairment of learning [88] and difficulties to comply with treatment [90] have also been suggested to explain nonresponse to OCD treatment among individuals with a schizotypal personality disorder. Moreover, OCD patients with a schizotypal personality disorder may respond better to low-dose atypical neuroleptics and specialized CBT for schizotypal symptoms [89]. Other personality disorders have been associated with a less favorable outcome of CBT among OCD patients. In one study [91], OCD patients with any Cluster A or Cluster B personality disorder showed a poorer response to behavioral treatment or CBT at 12-month follow-up, compared with patients without these diagnoses.

Some studies have found no effect of personality disorders on the outcome of CBT for OCD. Dreessen and colleagues [79] studied 43 OCD patients who completed a behavioral or cognitive treatment, or a CBT. The presence of one or more personality disorders had no impact on the outcome of treatment. Indeed, patients with personality disorders did not differ in their improvement from patients without a personality disorder, and they dit not differ on their end-state functioning. Moreover, those who abandoned treatment did not differ from completers with regard to personality disorder characteristics. In another study [80], influence of personality disorders on the outcome of CBT has been compared for 24 OCD patients with comorbid personality disorders, and 31 without a personality disorder. Results indicated that both groups benefited equally from treatment, and were able to maintain their improvement at follow-up. Steketee [77] also found no association between personality disorders and the outcome of a behavioral treatment for OCD. However, the author suggested that an unsufficient statistical power might have explained that no differences in outcome were found between patients with and without a personality disorder [77]. Surprisingly, a positive impact of personality disorder traits on treatment outcome was found: patients with dependent or avoidant personality traits had improved significantly

more on target symptoms at posttest. Yet, the improvement was not maintained during the follow-up period. No explanation was proposed for this unusual finding, and it should be carefully interpreted given the small sample size in this study (n=26).

5.3. Pharmacological treatment

The presence of a comorbid schizotypal personality disorder has also been associated with poorer outcome of pharmacological treatment [87, 90, 92], and of combined behavioral and pharmacological treatment [88] for OCD. In one study [93], the presence of schizotypal personality disorder, AVPD, or BPD, and the presence of any Cluster A diagnosis were associated with poorer outcome of a tricyclic antidepressant treatment (TCA) for OCD. Cavedini and colleagues [78] found a negative influence of OCPD on the outcome of a pharmacological treatment. Thus, poorer response to TCA or SSRI treatment was reported in OCD patients with OCPD than those without the comorbid Axis II diagnosis. However, one study [94] found no effect of personality disorders on the outcome of an SSRI medication for OCD. An association with outcome was only found for AVPD, which was associated with greater improvement on OCD symptoms.

6. Generalized Anxiety Disorder (GAD)

Studies have reported prevalence rates of personality disorders of 35% to 50% among patients with GAD [13, 95-98]. Compared with PD patients, GAD patients have been found to be more likely to have at least one personality disorder [13]. Similar to personality disorders, GAD seems to be more trait-like than state-like, since its symptoms are fairly continuous and lasting in time [13]. Thus, it has been suggested that personality disorders may be a more important factor in the development of GAD than they are for other anxiety disorders [13, 99]. Although GAD does not seem to have a strong association with a particular type of personality disorder [100], Dyck and colleagues [13] found AVPD to be the most prevalent (22%) in their sample of 122 GAD patients. Some correlations have also been found with obsessive-compulsive traits [101], OCPD [102], and dependent personality disorder [96].

6.1. Initial symtomatology and course of illness

There is an association between low social functioning and the presence of personality disorders among GAD population, although the relation seems to be specific to certain areas of functioning [103]. Indeed, results indicated no significant association between the presence of a personality disorder and functioning with mates, siblings, or functioning as a student. In addition, personality disorders were found to influence the naturalistic course of GAD. For instance, Ansell and colleagues [18] found that GAD patients with OCPD or BPD at baseline were more likely to have a GAD relapse, and those with OCPD were also more likely to have a new episode onset of GAD, compared with patients without these personality disorders. Also, schizotypal personality disorder was found to be the strongest predictor of chronicity, which was measured by the proportion of weeks spent in episode of GAD [18].

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In another study [95], the presence of AVPD or dependent personality disorder explained the lower probability of remission from GAD.

6.2. Influence of personality pathology on the outcome of cognitive and/or behavioral treatment for GAD

Very few studies have examined the effect of personality disorders on the outcome of CBT for GAD. The lack of treatment studies with GAD patients may be partly explained by the fact that this anxiety disorder was not officially recognized as a primary diagnostic category until the appearance of the DSM-III-R [104]. However, Sanderson, Beck, and McGinn [97] examined the effect of personality disorders on the immediate outcome of a cognitive therapy for 22 patients with GAD. Although there were no significant differences in improvement and end-state functioning in patients with and without personality disorders, patients with a comorbid personality disorder were more likely to drop out of treatment [97]. In addition, the Tyrer et al. study [52] mentioned previously found a negative influence of personality disorders on the outcome of CBT for GAD.

6.3. Pharmacological treatment

To our knowledge, very few controlled prospective studies have examined the link between the presence of a personality disorder and the outcome of pharmacological treatment for GAD. Although they did find an influence of personality disorders on the outcome of CBT, Tyrer and colleagues [52] found no effect of personality disorders on the outcome of pharmacotherapy for GAD. One retrospective study [102] examined the effect of personality disorders on the outcome of a benzodiazepine drug treatment for GAD. The results indicated that chronic GAD patients were more likely to have Cluster B or C disorders than were remitted GAD patients. However, it is impossible to assume that outcome is due to the original drug treatment because participants had not been assessed immediately after treatment. In fact, participants were only interviewed 16 months after treatment, and during the follow-up period, they have had different types of treatment, pharmacological or psychological. Also, personality disorders were not assessed before treatment [102]. Thus, based on these results only, it cannot be concluded that personality disorders have a negative effect on the outcome of pharmacological treatment for GAD.

7. Social phobia

The rate of personality disorder diagnoses has been reported to be generally higher among social phobic patients than among patients with other Axis I conditions [13, 15]. Among anxiety disorder patients, some studies have also found the highest rates of personality disorders to be among patients with social phobia [16, 98]. The prevalence of personality disorders among social phobic patients ranges from 24% to 56% [105-107]. A strong association has been found between social phobia and AVPD [107-110]. Indeed, Dyck and colleagues [13] results indicated that individuals with social phobia were more than two times more

likely to have an AVPD, compared with patients with PD or GAD. Overall, studies have reported 36% to 89% of comorbidity between AVPD and the generalized subtype of social phobia [13, 111-114]. In fact, questions have been raised about the validity of the existing categorical distinction between these two disorders [15, 23, 105]. Indeed, DSM-IV-TR criterion A for social phobia ("a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others; the individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing") overlaps with criterion four of AVPD ("the individual is preoccupied with being criticized or rejected in social situations"). In addition, DSM-IV-TR criterion D for social phobia ("the feared social or performance situations are avoided or else are endured with intense anxiety or distress") overlaps with criteria one ("avoids occupational activities that involve significant interpersonal contact, because of fears of criticism, disapproval, or rejection") and seven ("is unusually reluctant to take personal risks or to engage in any new activities because they may prove embarrassing") for AVPD. Furthermore, given that studies have found few cases of AVPD without generalized social phobia [115, 116], it has been suggested that AVPD could represent a subtype of more severe social phobia [15, 39]. In a review of literature on this subject, Widiger [116] concluded that there is no evidence indicating a clear demarcation between the two disorders, and that they appear to be a single disorder. Moreover, a recent twin study [117] found a common genetic vulnerability to women with AVPD and women with social phobia, which gives support to the hypothesis of a shared etiology. Even though the literature has focused on the association of social phobia with AVPD, other personality disorders have been found to be prevalent among social phobics. In their review, Johnson and Lydiard [15] reported OCPD and dependent personality disorder to be the second most prevalent among social phobics. Thus, social phobia seems to be particularly associated with Cluster C personality disorders.

7.1. Initial symptomatology and course of illness

In most studies, social phobic patients with comorbid personality disorders are reported to be more severely impaired before treatment. Mersch and colleagues [106] showed that social phobic patients with a comorbid personality disorder presented a more severe symptom pattern at baseline, with more irrational and negative thinking patterns, compared to those without a personality disorder. Moreover, two studies found more depressive symptoms for social phobic patients with personality disorders compared to those without an Axis II diagnosis [15, 107]. Herbert and colleagues [112] compared patients with generalized social phobia with and without AVPD, and found that patients with AVPD had more comorbid pathology, impairment in functioning, and reported higher levels of severity on all measures, including fear of negative evaluation, social avoidance and distress, depression and general psychopathology. Other studies have reported social phobic patients with a comorbid AVPD to have a more severe baseline symptomatology compared to those without an AVPD [111, 113]. In addition, the presence of a personality disorder, and more specifically an AVPD, has been associated with a decreased likelihood of remission from social phobia, when no treatment is considered [18, 95]. Patients with this comorbidity are also more likely to have a new episode onset of social phobia, in comparison to social phobics without an AVPD [18]. A comorbid AVPD was also found

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to be the strongest predictor of chronicity of social phobia [18]. Finally, the presence of a schizotypal personality disorder has been associated with an increased likelihood of social phobia relapse [18]. Given that it may be difficult to distinguish between long-standing social fears and Cluster A personality disorder symptoms, the latter finding could be explained by an erroneous assessment [115]. Thus, the social isolation would not be the result of a social anxiety, but rather a consequence of the paranoid thinking that generally characterizes an individual with a schizotypal personality disorder.

7.2. Influence of personality pathology on the outcome of cognitive and/or behavioral treatment for social phobia

Outcome studies have shown that there is no effect of personality disorders on the outcome of cognitive and/or behavioral treatment for social anxiety. For instance, a study [106] examining the outcome of two forms of treatment for social phobia, an exposure-based treatment or CBT, showed that patients with a comorbid personality disorder have been found to improve as much as those without a personality disorder. Another study [110] also indicated no differences on the outcome of a behavioral therapy with regard to the presence or absence of a comorbid personality disorder. Indeed, results indicated that patients with and without personality disorders improved at the same rate on social phobic avoidance, cognitions, and target situations that needed to be changed.

Because of its strong association with social phobia, many studies examined the specific effect of AVPD on the outcome of treatment. Feske and colleagues [111] examined its effect on the outcome of an exposure-based therapy for 48 patients with social phobia. Those with an AVPD improved less with regard to trait anxiety and self-esteem at posttest, but no differences in improvement rates were found with regard to depression, social adjustment and social phobic complaints. Although patients with an AVPD continued to have more severe symptomatology than those without AVPD at posttest and 3-month follow-up, both groups improved at the same rate during the follow-up period. However, the authors mentioned that interpretation of the follow-up data is difficult because of the additional uncontrolled treatments received during this period [111]. Other studies also reported no effect of AVPD on the outcome of cognitive and/or behavioral treatment for social phobia [110, 113, 118, 119]. Thus, evidence suggests no influence of AVPD on the outcome of CBT for social phobia.

To our knowledge, only one study [120] found a negative impact of personality disorders on the outcome of a cognitive and behavioral group treatment for social phobic patients. After treatment, patients without a personality disorder had improved significantly more on all outcome measures, except for the State-Trait Anxiety Inventory (STAI) and on the rating of avoidance of worst fear, for which there were no significant differences [120]. However, these results should be carefully interpreted, given that the effect sizes are very small for all of these outcome measures.

7.3. Pharmacological treatment

Very few studies have examined the impact of Axis II diagnosis on the outcome of pharmacological treatment for social phobia. To our knowledge, one study [121] has found a

negative influence of personality disorders on the outcome of a pharmacological treatment for social phobia. In this study [121], long-term treatment with moclobemide (monoamine oxidase inhibitor; MAOI) was investigated among 101 social phobic patients. Treatment consisted of four years of moclobemide, with a drug-free period of at least one month, after the first two years. Dependent personality disorder and AVPD were diagnosed in 16% and 72% of patients, respectively. Results indicated that Axis II diagnosis predicted non-response to moclobemide.

8. Posttraumatic Stress Disorder (PTSD)

High rates of personality disorders have been found among individuals with PTSD [122-124]. Studies have reported comorbid Axis II diagnosis in 39% to 45% of PTSD patients [125, 126]. A strong association has been found between PTSD and BPD [127, 128]. For example, Zanarini and colleagues [129] results indicated that PTSD was significantly more diagnosed among BPD patients than among patients with other personality disorders. Also, in a sample of 34 male combat veterans with PTSD, BPD was the most common Axis II diagnosis, with a prevalence rate of 76% [123]. Shea and colleagues [124] also reported high rates of BPD [68%) among PTSD patients.

Given that past events of traumatic exposure are commonly reported by individuals with BPD [130], a history of trauma has been proposed to have a formative role in the development of BPD [131-133]. However, a strong association between the two disorders has not been found consistently across studies. In two other studies [126, 134], only 10% of PTSD patients had a comorbid BPD. Hembree and colleagues [126] suggested that these low rates might be explained by the exclusion of patients with current suicidal plans or intentions, and those with self-injurious behaviors from both studies. Since these characteristics are commonly present among individuals with BPD, this could have possibly led to the exclusion of a significant amount of BPD patients in those studies.

8.1. Initial symptomatology and course of illness

PTSD patients with comorbid personality disorders may experience a more severe course of illness than PTSD patients without personality disorders [135]. More specifically, Ansell and colleagues [18] found that PTSD patients with a schizotypal personality disorder at baseline were less likely to remit from PTSD than patients without a schizotypal diagnosis [18]. Surprisingly, their results also suggest that the presence of an OCPD is associated with a positive course of illness for PTSD. Indeed, patients with an OCPD at intake were less likely to have a PTSD relapse [18]. This could be explained by the fact that OCPD is characterized by perfectionism, meticulosity, rigidity, and extreme devotion to work and efficiency (DSM-IV-TR), which may lead to a good compliance with treatment. As mentioned previously, although Ansell and colleagues [18] investigated the naturalistic course of anxiety disorders, they recruited their sample among a treatment-seeking population. Even though no treatment was controlled in this study, the patients still received some form of treatment during

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the 7-year period of the study. Thus, OCPD patients, because of their possibly good compliance with treatment, might have respond better to treatment for their PTSD, which might have led to a decreased likelihood of relapse.

However, most studies have specifically measured the impact of BPD on pretreatment symptomatology of PTSD patients. For instance, Axis I diagnoses were found to be more prevalent among individuals with coexisting PTSD and BPD, in comparison to individuals with PTSD alone [128]. A comorbid BPD diagnosis has also been associated with greater psychosocial impairment [128], and higher general distress [127, 136]. Moreover, studies have reported greater suicide proneness [128] among PTSD individuals with comorbid BPD, compared with PTSD individuals without BPD. Also, PTSD patients with comorbid BPD were reported to be more severely disturbed with regard to PTSD symptoms [127], although other studies did not find such differences between PTSD patients with and without comorbid BPD [136, 137]. Feeny and colleagues [134] also found no group differences on measures of anxiety, depression, and social functioning with regard to the presence or absence of partial, or complete BPD diagnosis.

8.2. Influence of personality pathology on the outcome of cognitive and/or behavioral treatment for posttraumatic stress disorder

As for other anxiety disorders, studies have yielded conflicting findings with regard to the effect of Axis II diagnosis on the outcome of CBT for PTSD. In the Hembree et al. [126] study, there were no significant differences between women with and without personality disorders on the prevalence of PTSD at the end of CBT or prolonged exposure. However, significantly more participants without a personality disorder (76%) achieved good end-state functioning status than participants with a personality disorder (41%). However, the group with personality disorders had higher scores on measures of PTSD symptoms, anxiety, and depression at pretreatment compared to the group without personality disorders, which could explain that this group was less likely to achieve a good end-state functioning [126]. In their retrospective study, Feeny and colleagues [134] examined the effect of borderline personality characteristics on the outcome of cognitive and/or behavioral therapy among 72 women with PTSD. Their results indicated that the group without borderline personality characteristics (described as having no significant BPD symptoms) had achieved a better end-state functioning at posttest, although this result was not obtained at the 3-month follow-up. However, there were no differences between groups on PTSD status, and outcome measures at posttest and follow-up [134].

In one study [138] examining predictors of outcome for PTSD patients treated with an exposure-based treatment, personality disorders were not found to predict treatment outcome, or premature dropout. In their retrospective study, Clarke and colleagues [127] found similar results with regard to borderline personality characteristics. Their results indicated that PTSD women with higher rates of borderline personality characteristics benefited as much from CBT, and that they were not more likely to drop out of treatment. To our knowledge, no study has examined the influence of personality disorders on the outcome of pharmacological treatment for PTSD.

Authors	Year	Participants	Treatment	Influence of personality disorders on outcome	Other results
Tyrer, Seivewright, Ferguson, Murphy, and Johnson	1993	181 patients with GAD, PD, or dysthymia	Pharmacotherapy, cognitive therapy, or self-help.	The presence of a personality disorder was associated with a poorer outcome of CBT and self–help at 2-year follow-up.	
Seivewright, Tyrer, and Johnson	1998	181 patients with GAD, PD, or dysthymia	Pharmacotherapy, cognitive therapy, or self-help.	The presence of a personality disorder predicted poorer outcome of CBT and self-help at 5-year follow-up.	
Panic disorder with and/or without agoraphobia					
Green and Curtis	1988	25 patients with PD/A (13 had at least one personality disorder)	Pharmacological treatment (alprazolam, imipramine, or placebo)	The presence of one or more personality disorder, and the presence of AVPD were associated wih relapse.	
Reich	1988	52 patients with PD/A (19 had at least one personality disorder)	Pharmacological treatment (alprazolam or diazepam)	The presence of antisocial, borderline, narcissistic, and histrionic personality disorders was associated with poorer outcomes on all measures, except for spontaneous panic attacks.	
Marchand and Wapler	1993	41 patients with PDA	CBT	No differences were found on outcome with regard to the presence or absence of a personality disorder.	
Keijsers, Schaap, and Hoogduin	1994	60 patients with PD/A	Behavioral treatment	As measured by PDQ-R scores, higher personality psychopathology was associated with higher levels of agoraphobic avoidance and higher frequency of panic attacks at posttest.	The relationship was no longer significant after adjusting for multiple tests.
Dreessen, Arntz, Luttels, and Sallaerts	1994 (1st study)	31 patients with PD/A (14 had at least one personality disorder)	CBT	No influence on outcome was found with regard to the presence of a personality disorder.	OCPD traits predicted worse outcome at posttest, 1-month, and 6-month follow-up. Borderline personality traits predicted better outcome at 6-month follow-up.

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Authors	Year	Participants	Treatment	Influence of personality disorders on outcome	Other results
Black et al.	1994	66 patients with PD/A (23 had at least one personality disorder when measured by SIDP-R, and 22 had at least one personality disorder when measured by PDQ)	Cognitive therapy, pharmacotherapy, or placebo.	The presence of a personality disorder was not a predictor of treatment outcome at week 4, when personality was assessed by the SIDP-R.	The presence of a personality disorder was a negative predictor of outcome at week 4 in groups receiving cognitive therapy or placebo, when personality was assessed by a self-report questionnaire (PDQ).
Fava et al.	1995	110 patients with PDA	Behavioral treatment	The presence of a personality disorder was associated with a decreased likelihood of remission for 7 years after treatment.	
Rathus, Sanderson, Miller, and Wetzler	1995	18 patients with PDA (10 had at least one personality disorder)	CBT	No differences were found on outcome measures with regard to the presence or absence of a personality disorder.	
Hofmann et al.	1998	93 patients with PD/A	CBT or pharmacotherapy	Personality disorder traits did not predict outcome of treatments.	
Chambless et al.	2000	49 patients with PDA (27% had AVPD)	Behavioral treatment	AVPD predicted less improvement in the frequency of panic attacks at the 6-month follow-up.	
Toni et al.	2000	326 patients with PD/A	Pharmacological treatment (antidepressants, mainly imipramine, clomipramine, and paroxetine)	Personality disorders were not associated with outcome of treatment.	
Berger et al.	2004	73 patients with PD/A (23 had at least one personality disorder)	Pharmacological treatment (paroxetine) or pharmacological treatment + cognitive therapy	The presence of a personality disorder, particularly AVPD, was associated with poorer response to treatment.	
Prasko et al.	2005	60 patients with PD/A (29 had at least one personality disorder)	Pharmacological treatment (SSRI) + CBT (15 patients received CBT only)	The presence of a personality disorder was associated with poorer outcomes on most measures.	There were no differences on overall symptoms of anxiety, with regard to the presence or absence of a personality disorder.

Authors	Year	Participants	Treatment	Influence of personality disorders on outcome	Other results
Marchesi et al.	2006	71 patients with PD/A (38 had at least one personality disorder)	Pharmacological treatment (paroxetine or citalopram)	BPD traits were negatively associated with remission of panic attacks	
Kampman, Keijsers, Hoogduin, and Hendriks	2008	161 patients with PD/A (of the 129 completers, 60 had at least one Cluster C personality disorder, and 47 had AVPD)	CBT	The presence of Cluster C personality disorders was not associated with outcome of treatment.	
Telch, Kamphuis, and Schmidt	2011	173 patients with PD/A (54 had at least one personality disorder)	CBT	The presence of one or more personality disorders was associated with a poorer outcome of CBT at posttest, when baseline severity of panic disorder was not controlled.	When baseline severity was controlled, Cluster A and C personality disorders were associated with poorer outcome. When assessed dimensionally, only Cluster C traits were associated with poorer outcome.
Obsessive-compulsive disorder					
Jenike, Baer, Minichiello, Schwartz, and Carey	1986	43 patients with OCD (14 with a schizotypal personality disorder and 29 without a schizotypal personality disorder)	Pharmacotherapy, Behavior therapy, or a combination of both	The presence of a schizotypal personality disorder predicted poorer response to both types of treatment.	
Minichiello, Baer, and Jenike	1987	29 patients with OCD (10 with a schizotypal personality disorder and 19 without a schizotypal personality disorder)	Behavioral treatment or Behavioral treatment + Pharmacological treatment	The presence of a schizotypal personality disorder was negatively associated with outcome.	The number of schizotypal traits was also negatively associated with outcome.
Steketee	1990	26 patients with OCD (13 had at least one	Behavioral treatment	Personality disorders were not associated with treatment outcome.	Dependent and avoidant traits were

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Authors	Year	Participants	Treatment	Influence of personality disorders on outcome	Other results
		personality disorder)			associated with better outcomes.
Baer and Jenike	1990	67 patients with OCD	Pharmacological treatment (fluoxetine)	The presence of an AVPD was associated with more improvement on OCD symptoms.	
Baer et al.	1992	55 patients with OCD (33 had at least one personality disorder)	Pharmacological treatment (clomipramine)	The presence of schizotypal personality disorder, AVPD, and BPD was associated with poorer outcomes.	The presence of any Cluster A diagnosis, and the number of personality disorders diagnosed were associated with poorer outcomes.
Maina, Bellino, and Bogetto	1993	48 patients with OCD (44 had at least one personality disorder)	Pharmacological treatment	Number of personality disorders diagnosed, and the presence of a schizotypal personality disorder were associated with chronicity of OCD	
Ravizza, Barzega, Bellino, Bogetto, and Maina	1995	53 patients with OCD (28% (n=15) had a schizotypal personality disorder)	Pharmacological treatment (clomipramine or fluoxetine)	The presence of a schizotypal personality disorder was associated with nonresponse to treatment.	
Cavedini, Erzegovesi, Ronchi, and Bellodi	1997	30 patients with OCD (9 with an OCPD and 21 without an OCPD)	Pharmacological treatment (clomipramine or fluvoxamine)	The presence of an OCPD predicted poorer treatment outcome.	
Dreessen, Hoekstra, and Arntz	1997	52 patients with OCD (of the 43 completers, 22 had at least one personality disorder)	Behavior therapy, Cognitive therapy, or CBT	Personality disorders were not associated with outcome of treatment.	
Fricke et al.	2005	55 patients with OCD (24 had at least one personality disorder)	CBT	The presence of a personality disorder was not associated with treatment outcome.	
Hansen, Vogel, Stiles, and Götestam	2007	35 patients with OCD (24 had at least one personality disorder)	CBT or Behavior therapy + relaxation training	The presence of Cluster A or B personality disorders was associated with poorer outcomes at 12-month follow-up, in both treatment conditions.	

Authors	Year	Participants	Treatment	Influence of personality disorders on outcome	Other results
Generalized anxiety disorder					
Mancuso, Townsend, and Mercante	1993	44 patients with GAD	Pharmacological treatment (adinazolam or placebo)	The presence of a personality disorder, particularly in Cluster B or C, was negatively associated with remission 16 months after treatment.	
Sanderson, Beck, and McGinn	1994	22 patients with GAD (9 had at least one personality disorder)	Cognitive therapy	Personality disorders were not associated with treatment outcome.	Patients with personality disorders were more likely to drop out of treatment.
Social phobia					
Turner	1987	13 patients with social phobia (7 had at least one personality disorder)	CBT	Patients with personality disorders improved less on most outcome measures during treatment.	
Mersch, Jansen, and Arntz	1995	34 patients with social phobia (8 had at least one personality disorder)	Behavioral treatment or CBT	Personality disorders did not influence the outcome of treatment.	
Hofmann, Newman, Becker, Taylor, and Roth	1995	16 patients with social phobia (8 with an AVPD and 8 without an AVPD)	Behavioral treatment	Patients with and without an AVPD improved as much with treatment.	
Brown, Heimberg, and Juster	1995	102 patients with social phobia (28 with an AVPD and 74 without an AVPD)	CBT	The presence of an AVPD did not predict treatment outcome.	
Hope, Herbert, and White	1995	23 patients with social phobia (14 with an AVPD and 9 without an AVPD)	CBT	The presence of an AVPD did not predict treatment outcome.	
Feske, Perry, Chambless, Renneberg, and Goldstein	1996	48 patients with generalized social phobia (35 with an AVPD and 13 without an AVPD)	Behavioral treatment	The presence of an AVPD was associated with less improvement on trait anxiety and self-esteem during treatment, but no differences were found with regard to depression,	However, patients with an AVPD continued to be more severely impaired at posttest and follow-up. When baseline depression was

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Authors	Year	Participants	Treatment	Influence of personality disorders on outcome	Other results
				social adjustment and social phobic complaints. Patients with and without an AVPD improved at the same rate during the follow-up period.	controlled, AVPD no longer predicted improvement during treatment.
Versiani et al.	1996	101 patients with social phobia	Pharmacological treatment (moclobemide)	Personality disorders predicted nonresponse to treatment.	
Van Velzen, Emmelkamp, and Scholing	1997	61 patients with social phobia (30 without any personality disorder, 18 with an AVPD, and 13 with multiple personality disorders)	Behavioral treatment	Personality disorders did not influence the outcome of treatment.	
Posttraumatic stress disorder					
Feeny, Zoellner, and Foa	2002	72 women with PTSD (7 with complete BPD diagnosis, 5 with partial BPD diagnosis, and 60 without a BPD)	Cognitive therapy, behavior therapy, or CBT	There were no differences between patients with and without BPD characteristics with regard to PTSD status, and measures of PTSD symptoms, anxiety and depression after treatment.	The presence of BPD characteristics was associated with a decreased likelihood of achieving good end-state functioning at posttest.
van Minnen, Arntz, and Keijsers	2002	122 patients with PTSD	Behavioral treatment	Personality disorder traits were not associated with treatment outcome, or premature termination of treatment.	
Hembree, Cahill, and Foa	2004	75 women with PTSD (29 had at least one personality disorder)	Behavioral treatment or CBT	Personality disorders did not influence the prevalence of PTSD diagnosis at posttest.	Patients with a personality disorder were less likely to achieve a good end-sate functioning after treatment.
Clarke, Rizvi, and Resick	2008	131 women with PTSD	Cognitive therapy or behavior therapy	Patients with higher BPD characteristics benefited as much from treatment.	

Table 1. Studies examining the influence of personality disorders on the outcome of CBT and/or pharmacological treatment for anxiety disorders

9. Mechanisms underlying the influence of personality disorders on treatment for anxiety disorders

Many arguments have been reported to explain the negative impact of personality disorders on the outcome of treatment for anxiety disorders. For instance, adverse life events have been found to be related to symptoms of anxiety and depression, and in many of those events, the individual is actively involved in both the onset and termination of the event [139]. Thus, personality disordered patients may create more negative life events for themselves, which contribute to chronic psychosocial dysfunction and increased stress [139], which in turn can negatively affect treatment outcome [32]. In addition, it has been argued that part of the differences in outcome between patients with and without personality disorders may be explained by higher drop-out rates among patients with comorbid personality disorders [32, 140]. Indeed, patients with personality disorders may experience less emotional improvement during cognitive therapy than patients without personality disorders [141]. Thus, these patients may drop out of treatment because they perceive therapy sessions as being less effective [142]. Given that compliance with treatment regimens as rated by the therapist has been associated with positive outcome of CBT for anxiety disorders [143], anxiety patients with personality pathology might comply less with treatment, which would negatively affect the outcome of intervention or lead to premature drop-out. Finally, as mentioned previously, patients with coexisting anxiety and personality disorders have been reported to have higher initial levels of symptomatology compared with anxiety patients without a personality disorder, which could account for the difference in results when baseline severity is not controlled in the analysis. When a person reports more severe symptoms at baseline, we could expect that this person would still remain more symptomatic after treatment, even though she might have improved at the same rate. In fact, the severity of symptoms before treatment has been found to predict the outcome of treatment for anxiety disorders. In one study, this baseline symptomatology has been found to be a strong predictor of end-state functioning at the 3-year follow-up test [46]. In the Telch et al. [38] study, initial levels of PD severity accounted for 27% of the explained variance in clinically significant change at posttreatment. Yet, after controlling for baseline severity of PD, results indicated that the presence of a Cluster A personality disorder still had a significant negative effect on treatment outcome, although the relationship was very modest [38].

10. Effect of treatment for anxiety disorders on personality functioning

There is evidence suggesting that treatment for Axis I disorders reduces Axis II disorders and traits. For example, Ricciardi and colleagues [144] reported that 90% of responders to OCD pharmacological and/or behavioral treatment no longer met criteria for a personality disorder, mostly avoidant, dependent, or obsessive-compulsive personality disorder. Some authors have argued that improvement of personality functioning with treatment for anxiety disorders is explained by the instruments used to assess personality, which may confound Axis I and Axis II disorders [145] or be unable to distinguish between abnormal personality traits and personality

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disorder symptoms [146]. Also, as mentioned previously, assessment of personality may be affected by the presence of Axis I disorders, which would explain improvement in personality functioning with improvement of OCD symptoms [144]. In addition, three studies [147-149] have found a reduction of avoidant personality traits after pharmacological treatment for social phobia. However, most of the studies that examined changes in personality functioning with anxiety disorder treatment were conducted among patients with PD. Thus, improvement in personality functioning with cognitive and/or behavioral treatment for PD has been demonstrated more than once [61, 62, 146, 150, 151]. For instance, PD patients treated with CBT have been reported to show significant decline in all personality disorder subscales, with the exception of schizoide personality traits, from pretreatment to the second assessment (after the 11th session; [62]). However, the decline from the second to the third assessment (six months after the second assessment) was not significant for any of the subscales, except for the Schizoid Personality Disorder Scale, even though patients had received six additional monthly maintenance sessions during this period. Although these results were obtained when responders and nonresponders were combined, responders to CBT were found to have greater improvement in personality disorder characteristics than nonresponders to CBT [62]. In another study [150], an 82% decrease of personality disorder traits has been found among PD patients treated with cognitive therapy. Pharmacological treatment for PD has also been demonstrated to improve personality disorder characteristics [36, 62]. For example, in Marchesi et al. study [36], the rate of personality disorders has been found to decrease from 60% before treatment to 43% after treatment, and these results were mainly due to the reduction in the rate of paranoid, avoidant and dependent traits. The results obtained in these studies do not necessarily indicate that personality changes that occur after successful treatment for anxiety disorders result in a return to premorbid function [23]. Indeed, there is some evidence suggesting that these patients' personalities still remain differentiable from normal controls [152]. Many suggestions have been made to explain the possible influence of anxiety disorder treatment on personality pathology. First, abnormal personality traits may be a consequence of living with an anxiety disorder [36, 61]. Thus, the personality dysfunction may decrease with the improvement of anxiety disorder symptoms. Second, an interaction or overlap of Axis I and Axis II symptoms may explain the improvement of personality dysfunction with successive treatment for Axis I disorders [20]. Third, CBT for anxiety disorders could provide general problem-solving skills to the patients, which could decrease pathological personality dysfunction [62]. In addition to the confounding assessment of personality in the presence of Axis I disorders that was reported earlier, methodological limitations may have led to these results. For example, in the Ricciardi et al. study [144], the very small sample size (n=10) may have increased the risk of type I error. Thus, we cannot exclude the possibility that their findings are only due to chance fluctuations.

11. Issues to consider in therapy

Studies have yielded conflicting conclusions regarding the influence of Axis II diagnosis on the outcome of treatment for anxiety disorders. However, anxiety patients with comorbid personality disorders were consistently reported to improve on their anxiety disorder symp-

toms with treatment for their anxiety disorder, even though they did not always improve as much as patients without Axis II comorbidity. Therefore, these patients should not be excluded from treatment for their anxiety disorder, because of their comorbid diagnosis [33]. Also, clinicians should be aware of their own attitude towards patients with personality disorders, given that the therapist's belief that patients with a comorbid personality disorder will not benefit from any therapy, might initiate a self fulfilling prophecy [33]. In addition, to reduce the probability of early termination of treatment among patients with comorbid personality disorders, clinicians should identify these patients early in therapy, and frequently give feedback about the therapeutic process [142]. Since most individuals with personality disorders have major issues in their interpersonal relationships, it may be difficult to establish a solid therapeutic alliance. Thus, when working with patients with dysfunctional personality, it is often necessary to monitor patients' expectation with regard to the therapeutic relationship, to be flexible in using various relationship-building techniques, to identify the inevitable "ruptures" that occur in any therapeutic context, and to work to repair such ruptures when they occur [153]. Also, the dysfunctional attitudes[1] that are central to specific personality disorders should be discussed as a first step in therapy, given that they have a functional relation to anxiety, and that the development of some ego-dystony concerning attitudes is necessary for a specific anxiety treatment to be useful [155]. Finally, when working with patients with severe personality disorders, it is recommended to use a team-based treatment approach, since it may become emotionally too difficult for an individual therapist alone to treat patients with socially disruptive behaviors, such as parasuicide, and verbal and physical aggressions [153]. Moreover, patients' interactions with several professionals could enhance the acquisition of the adaptative skills taught in therapy. Special considerations in therapy should extend to individuals who consult for their personality disorder. Indeed, when patients present a history of anxiety disorders, treatment for personality disorders should be adapted to prevent the recurrence of anxiety disorder symptoms [18].

12. Plausible explanations for conflicting results

Some of the conflicting results that were presented in this chapter may be explained by methodological flaws in the existing studies, such as low statistical power (given the small sample sizes in many studies), failure to control for baseline severity of Axis I pathology, and the use of questionnaires to assess personality dysfunction [33]. Indeed, the use of a self-report questionnaire to assess personality pathology has been criticized. Compared to interviews, self-report questionnaires would be more sensitive to state factors, such as anxiety and depression, which would lead to a higher number of personality disorder diagnosis, particularly among individuals with Axis I disorders [33]. However, results from Black and colleagues [59] are not consistent with this, given that one more patient (23 vs 22) was diag-

1 Negatively biased assumptions and beliefs regarding oneself, the world, and the future. [154]

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nosed with at least one personality disorder when an interview was used to assess personality instead of a self-report questionnaire.

Furthermore, two of the studies [79, 97] reported in the Dreessen and Arntz review [33] as having yielded negative findings showed a strong trend for a higher level of personality pathology in drop-outs than in completers [32]. This may indicate that there was a negative effect of personality pathology in these studies, which was manifested in the drop-out rates [32]. Finally, the general conclusions drawn from the Dreessen and Arntz review [33] should be carefully interpreted. Indeed, some studies were reported as having no effect of personality on outcome, although when examined separately, there was at least a moderate effect [32]. As mentioned by Reich [32], it was reported in the review that Dreessen and colleagues [58] obtained negative results, although obsessive-compulsive personality traits were related negatively to treatment outcome, and they reported negative findings for the Black et al. [59] study when it was actually concluded that the presence of a personality disorder was a predictor of poor outcome in the non SSRI-treated group when the self-report questionnaire was used to assess personality pathology.

13. Future area of research

Even though studies have yielded conflicting conclusions regarding the influence of Axis II diagnosis on the outcome of treatment for anxiety disorders, most studies examining the outcome of treatment for PD and OCD have found at least some influence of personality disorders on CBT or pharmacotherapy outcome. However, personality disorders were generally found to have no influence on the outcome of CBT for social phobia and PTSD. Yet, most studies on social phobia and PTSD exclusively examined the influence of specific personality disorders, AVPD and BPD, respectively, and little is known about the influence of personality disorders in general on treatment outcome for these anxiety disorders. No conclusions can be yielded from GAD studies, given that, to our knowledge, only three studies have examined the influence of personality disorders on treatment outcome for GAD, and that one of these had serious methodological limitations. Furthermore, the mechanisms that underlie the effect of Axis II disorders on the outcome of treatment for anxiety disorders are not strongly established. Future studies should concentrate on studying well reasoned hypotheses concerning these mechanisms [33] so that responsible personality variables could be understood, and intervention adapted for the needs of this specific population. For instance, the associations in course between anxiety and personality disorders may be explained by personality traits, which underlie both disorders [18], and examining these maladaptive personality traits could help us understand better the underlying mechanisms that explain the influence of personality on anxiety disorders. Although some studies have examined the influence of personality disorder traits on treatment outcome of anxiety disorders, different results have been obtained when personality was assessed dimensionally instead of categorically. In addition, improvement in the evaluation of personality is needed, to eliminate, or at least decrease, the overlap of Axis I and Axis II criteria. There is also a need for more consistency in the methods used to assess personality disorders, given that

different results were obtained when personality was assessed by a self-report questionnaire instead of an interview. Further research is needed to determine whether patients with comorbid personality disorders could attain levels of posttreatment functioning equal to anxiety patients without personality dysfunction by varying duration and/or intensity of treatment sessions [38, 106], or by combining different treatment modalities [80]. Finally, more controlled prospective studies with larger sample sizes are needed to better understand the influence of personality disorders on anxiety disorders, particularly for GAD, given the small number of studies conducted among individuals with this anxiety disorder.

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Section 4

Therapies: New Approaches and Insights

Chapter 13

Treatment of Generalized Anxiety Disorders: Unmet Needs

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Additional information is available at the end of the chapter

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1. Introduction

Generalized anxiety disorder (GAD) is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as the presence of persistent, excessive anxiety and worry about a number of events and activities occurring on most of the days for at least 6 months. The patient must also experience at least three of the following six symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance.

GAD has a 12-month prevalence of 1% – 2.1% and a lifetime prevalence of 2.8% – 4.1% in Europe and in the US (Grant et al., 2005), often occurs early in life with twice the number of women suffering from it compared to men (ESEMeD/MHEDEA Investigators, 2000). GAD is chronic and disabling, and is associated with high rates of psychiatric comorbidity and substantial personal, social and economic costs (Wittchen et al., 1994; Ballenger et al., 2001; Wittchen, 2002). Evidence shows GAD's impact on social functioning, distress levels, and utilization of medical care is equivalent to those of other major psychiatric disorders (Mennin et al. 2004). In the National Comorbidity Survey, Wittchen and colleagues found that ~38% of patients with GAD may have another anxiety disorder and 48% may have major depression in addition to GAD (Wittchen et al., 1994). In addition to psychiatric comorbidities, patients with anxiety disorders have a higher risk for developing medical diseases in the areas of cardiovascular, gastrointestinal and respiratory as compared with control groups (Bowen et al., 2000).

Remission criteria defined by Ballenger include no or minimal symptoms of anxiety (Hamilton Anxiety Scale score ≤7-10), no functional impairment (Sheehan Disability Scale score ≤1 on each item) and no or minimal symptoms of depression (Hamilton Depression Scale score ≤7) for generalized anxiety disorder (Ballenger, 1999). Remission rates are considerably low

in generalised anxiety disorder. Yonkers and colleagues have shown that the remission rates are only 15% and 25% among 164 patients after one and two years respectively (Yonkers et al., 1996). The probability of remission of GAD is only 38% at 5 years, and the probability of relapse after remission is 27-39% by 3 years (Yonkers et al., 2000).

GAD is often unrecognized or misdiagnosed as a physical condition due to the range of clinical presentations, including somatic symptoms, and the frequent occurrence of comorbid conditions. The main treatment approaches for GAD comprise pharmacotherapy or psychotherapy or a combination of both. The chronic and disabling nature of GAD often means that some individuals may fail to respond fully to first-line treatment (Bandelow et al., 2008; Goodwin et al., 2002; Altamura et al., 2008; Allgulander et al., 2002; Baldwin et al; 2005). Patients may therefore require a sequential trial of treatments or possibly a combination therapy (Davidson et al; 2010).

Research in the treatment of GAD has primarily focused on the efficacy of pharmacotherapy. Antidepressant and anxiolytic drugs are the two most commonly used pharmacological treatments for anxiety disorders. Newer anticonvulsant and sometimes antipsychotic drugs are also used in the treatment of some anxiety disorders including generalized anxiety disorder. More recently, there has been an increasing interest in the efficacy of psychotherapy. Of all the therapies, cognitive behavioral therapy (CBT) has established the most empirical support as an effective treatment for GAD (Gould et al. 2004).

In recent years, GAD-related disability (Wittchen, 2002) as well as impairment in quality of life and functioning has gain importance. Anxiety disorders result in considerable economic loss both decreasing working performance and increasing the number of applications for health care services (Wittchen, 2002; DuPont et al., 1996; Greenberg et al., 1999). GAD poses both personal and public substantial economic and social burden (Pollack et al., 2009).

According to the preliminary findings of our ongoing study on the evaluation of patient burden due to wrong diagnosis and treatment in patients with generalized anxiety disorder (GAD), the mean duration of GAD was 5.6±6.1 years, and the patients received initial treatment for their GAD 27.6±36.7 for months ago. It was noted that GAD was mostly accompanied by major depression (60.5%), followed by other anxiety disorders (31.6%). Of the patients diagnosed with GAD, 86.4% were using medication for GAD and 40.9% were admitted to an emergency service for any reason within the last 6 months. The mean number of emergency admissions was 3.1±3.7. Of the patients admitted to emergency services, 51.9% underwent analyses such as blood analysis, radiological examination, electrocardiography (ECG) and ultrasonography (USG), and 48.5% were referred to another specialist for consultation. The preliminary findings of the present study indicate that admissions of GAD patients to emergency services due to various complaints continue when these patients are not treated adequately and sufficiently, and that financial burden of this disorder increases incrementally due to laboratory analyses and imaging techniques, consultations and additional therapies performed during these admissions (Dilbaz and Karamustafalıoğlu 2012a).

This chapter presents the unmet needs in the treatment of generalised anxiety disorders and new strategies in treatment for GAD.

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2. Treatment

The primary goal of treatment of GAD is to alleviate psychic and somatic complaints, promote sleep, improve patient's functioning and enhance patient quality of life. Besides, treating other concomitant medical conditions (psychiatric and/or medical co-morbidity) and consequently providing remission and preventing relapses are also aimed. The important requirements for the therapy drug include rapid action, broad spectrum, increasing remission rates, preventing relapses, absence of symptoms due to discontinuation of drug, minimum interaction with other drugs, and safety for elderly and children (Dilbaz et al., 2011; Davidson et al., 2010). Treatment of GAD comprises drug therapy together with behavioral therapy and psychotherapy. Characteristics and severity of symptoms, co-morbidities, presence of substance addiction and risk for suicide, results of previous therapies, costs, availability of drug and patient preference should be considered while planning GAD treatment (Davidson et al., 2010).

2.1. Pharmacological strategies

2.1.1. Benzodiazepines

Many randomized, double-blind trials have demonstrated the efficacy of benzodiazepines in the acute treatment of GAD (Greenblatt et al., 1983; Rickels et al., 1987; Hollister et al., 1993). However, there is evidence that more than a third of patients will not meet remission criteria in the treatments with benzodiazepines (Shader and Greenblatt, 1983).

The risks and benefits of using benzodiazepines should be carefully considered in each patient. Benzodiazepines have rapid onset, relatively low toxicity, and anxiolytic potency but these benefits should be weighed against for potential motor impairment, dependence and withdrawal symptoms esspecially when prescribed for >4 weeks (Rynn and Brawman-Mintzer, 2004).

Particularly in older people, benzodiazepine use can be problematic due to side effects such as falls, memory impairment, incoordination, drowsiness, and confusion (Petrovic et al., 2003). They can also disrupt sleep architecture, and rebound insomnia may occur after stopping treatment (Longo and Johnson, 2000).

2.1.2. Antidepressants

Selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenalin reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs, particularly imipramine), and, in a single controlled trial, trazodone have demonstrated efficacy in treatment of GAD compared to placebo (Rickels et al., 1993). Several analyses have shown similar efficacy among antidepressant agents in the management of GAD (Kapczinski et al, 2003).

2.1.2.1. SSRIs and SNRIs

Of these, SSRIs and SNRIs are the recommended first-line drugs for treatment of anxiety based on strength of evidence and acceptable tolerability. Antidepressants, particularly SSRI, may be associated with an initial worsening of anxiety symptoms in some patients. A retrospective cohort study defined characteristics of patients which developed emergent anxiety following an antidepressant intiation as young age, white and women sex (Li et al., 2011). Li et al. also found that receiving bupropion, fluoxetine or sertraline had lower risk of anxiety development than citalopram, paroxetine, venlafaxine and mirtazapine (Li et al, 2009). It is recommended to start on low doses and slowly titrate up to a therapeutic dose to reduce these "activation" symptoms (Sinclair et al., 2009). Patients should be advised of the potential for initial increase/worsening of symptoms and the likely delay of clinical effect (some response often seen by 4 weeks). Patient awareness of these factors when commencing SSRI treatment assists in reducing early discontinuation of treatment. Concomitant use of benzodiazepines during early treatment with SSRI may be useful in moderating these "activation effects" of SSRI early in treatment, although the potential for dependence must be considered. SSRI need to be taken for up to 12 weeks in order to assess a patient's response to treatment. Dosing requirements (like initiation in lower doses and reaching optimal doses by weekly increments) for antidepressants differ to that needed in the treatment of depression. All patients being treated with antidepressants (irrespective of diagnosis) should be monitored for worsening of their clinical condition and the emergence of suicidal ideation (Anxiety Disorders – Drug Treatment Guidelines, 2008)

According to Western Australian Psychotropic Drugs Committee; sertralin, escitalopram and venlafaxin have second line of evidence in treatment of generalized anxiety disorders whereas paroxetine has first line evidence (Hidalgo et al., 2007; Kapczinski et al., 2003; Anxiety Disorders – Drug Treatment Guidelines, 2008). There was a small statistically significance in favour of escitalopram compared with paroxetine based on a reduction in HAM-A scores. In addition, there was a 40% reduction in risk of non-response and lower risk (although not statistically significant) of discontinuation of treatment due to adverse events for escitalopram compared with paroxetine (Baldwin et al., 2006). There were no statistically significant differences found between paroxetine and sertraline on any outcomes (Ball et al., 2005).

There were no differences found on reduction of anxiety symptoms between escitalopram and venlafaxine while venlafaxine was associated with a greater risk of discontinuation (although this was not statistically significant) (Bose et al., 2008). Duloxetine was found to be effective in 60-120 mg/d doses in treatment of generalised anxiety disorder when compared to placebo (Rynn et al., 2008; Hartford et al., 2007). No difference was found between duloxetine and venlafaxine for reduction in anxiety and discontinuation due to adverse events (Nicolini et al; 2009).

2.1.2.2. Bupropion

Bystritsky and colleagues compared bupropion XL and escitalopram in 24 patients with generalised anxiety disorder in a 12-week, double-blind, randomized controlled trial and reported comparable efficacy between bupropion and escitalopram (2008).

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2.1.2.3. Agomelatine

The efficacy of 25 to 50 mg/day agomelatine in generalised anxiety disorder (GAD) was assessed in a 12-week double-blind, placebo-controlled study of 121 patients with no comorbid disorders (Stein et al., 2008). Agomelatine was found more effective than placebo at reducing anxiety (based on Hamilton rating scale for Anxiety; p=0.04). Agomelatine also improved sleep symptoms, sleep latency (p≤0.001), quality of sleep (p=0.002) and awakenings (p≤0.0001).

2.1.3. Anticonvulsants

2.1.3.1. Valproate

Valproate has been investigated for the management of GAD in a double-blind, placebo-controlled randomized trial involving 80 male patients with GAD in a double-blind placebo-controlled design (Aliyev and Aliyev, 2008). 40 patients randomized to receive 500 mg valproate three times per day and 40 patients received mathed plasebo. At week 4, valproate separated from placebo by mean total HARS score, and at 6 weeks, the mean change in HARS score reached significance. The most common side effects in the valproate group were dizziness and nausea and further investigation is recommended.

2.1.3.2. Gabapentine

Pollack and colleagues reported two cases documenting improvements in patients with GAD, following addition of gabapentin to their treatment (Pollack et al., 1998).

2.1.3.3. Tiagabine

There are case series documenting patients with generalised anxiety disorder treated with tiagabine successfully (Schwarts, 2002; Crane et al., 2003; Schaller et al., 2004). Schwartz et al followed up 17 patients with GAD in an 8-week, open-label trial of tiagabine (mean dose 13 mg/d) augmentation to SSRIs or benzodiazepines. 76% of patients responded [≥ 50% reduction in anxiety symptoms (HARS)] and 59% achieved remission (HARS score ≤ 7) (Schwartz et al., 2005).

Pollack et al reported on 3 large 10-week, randomized, double-blind, placebo-controlled, parallel-group studies. In the fixed-dose study, 910 patients received 4, 8, or 12 mg/d of tiagabine and in two flexible-dose studies, a total of 920 participants were enrolled. The mean doses of tiagabine were 8.9 and 9.2 mg/d. Neither study found significant differences in anxiety symptoms (HARS used) when compared to placebo and investigators concluded that these studies do not support the efficacy of tiagabine in adult patients with GAD (Pollack et al., 2008).

2.1.3.4. Pregabaline

There have been several industry-sponsored, multicenter, outpatient, prospective, randomized, double-blind, placebo-controlled studies. Pande et al. showed a significant improvement with pregabalin compared to placebo, but no significant differences in response were observed when comparing pregabalin 50 mg tid to pregabalin 200 mg tid or lorazepam to pregabalin 200 mg tid. The most commonly associated adverse events with pregabalin were dizziness, somnolence, and headache (Pande et al., 2003). Feltner and colleagues also compared pregabalin (in different doses), lorazepam 2 mg tid, or placebo. They also found pregabalin 200 mg tid effective in treatment of GAD, however, pregabalin 50 mg tid wasn't effective and 200 mg tid was not significantly different from lorazepam (Feltner et al., 2003). Pohl et al. found pregabalin in 100 mg bid, 200 mg bid, and 150 mg tid doses significantly effective than in reducing anxiety symptoms (Pohl et al., 2005).

In another large study of 454 participants with GAD, Rickels et al. compared pregabaline (in different doses) with alprazolam and placebo. Investigators reported that of the 5 treatment groups, the 300-mg pregabalin group was the only medication group that differed statistically in global improvement at treatment end point not only from the placebo group but also from the alprazolam group (Rickels et al., 2005). Another study found pregabaline (400-600 mg/day) effective in treatment of GAD compared to placebo and safer than venlafaxine (Montgomery et al., 2006).

Lydiard et al combined data from 6 short-term, double-blind, placebo-controlled, fixed-dose trials of pregabalin for the treatment of GAD. They concluded that pregabalin had significant efficacy in treating both HARS psychic and somatic anxiety measures. Furthermore, they indicated that a dose-response effect was evident for pregabalin that appeared to reach a plateau at a dose of 300 mg/d (Lydiard et al., 2010).

Pregabalin is promising in both add-on and switch therapies in treatment-resistant GAD cases. Pregabalin rapidly (within days) relieves anxiety symptoms providing substantial advantage over SSRI and SNRIs (Dilbaz and Karamustafalıoğlu, 2012a).

2.1.3.5. Levetiracetam

One case with GAD reported by Pollack, had improved with levetiracetam 250 mg/d added to citalopram treatment (Pollack, 2002).

2.1.4. Atypical antipsychotics

Some first-generation antipsychotics were approved for a condition similar to GAD, and recent studies have suggested that atypical antipsychotics may also have a role in GAD. A Cochrane metaanalysis reported that nine studies investigated the effects of second-generation antipsychotics in generalised anxiety disorder. Seven of them investigated the effects of quetiapine. Participants with generalised anxiety disorder responded significantly better to quetiapine than to placebo (4 RCTs, N = 2265, OR = 2.21, 95% CI 1.10 to 4.45). However, patients on quetiapine arm were more likely to drop out due to adverse events, like gain weight or

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sedation. When quetiapine was compared with antidepressants in GAD, there was no significant difference in efficacy-related outcomes, but more participants in the quetiapine groups dropped out due to adverse events.

2.1.4.1. Quetiapine

Several preliminary reports of monotherapy trials of quetiapine versus placebo have described efficacy at doses in the range of 50–150 mg/d (Chouinard et al., 2008; Khan et al., 2008; Joyce et al., 2008; Bandelow et al., 2009), but quetiapine cannot yet be recommended as a routine GAD treatment until a full description of efficacy and safety from these studies have been published. However, the use of quetiapine could be considered after other classes of drugs have proved ineffective or when certain types of symptoms are present like insomnia.

2.1.4.2. Olanzapine

Pollack investigated olanzapine augmentation to fluoxetine at a mean dose of 8.7 mg daily and reported that olanzapine may be helpful for patients who fail to respond to SSRIs alone, considering the advers events like wight gain (Pollack et al., 2006).

2.1.4.3. Aripiprazole

Two studies demonstrate that aripiprazole has promise in augmentation at dosages starting at 10 mg daily (Menza et al., 2007; Hoge et al., 2008).

2.1.4.4. Risperidone

Adjunctive risperidone could be tried in patients with poor response at titrated doses up to 3 mg daily (Brawman-Mintzer et al., 2005; Simon et al., 2006).

2.1.4.5. Ziprasidone

Ziprasidone at a daily dose range of 20 to 80 mg may be helpful for patients with GAD who did not have an adequate response to other medication treatment (Snyderman et al., 2005).

2.1.5. Other drugs

2.1.5.1. Azapirones

Buspirone was approved for the treatment of GAD more than 20 years ago. In recent years, multiple members of the azapirone class, which comprises the partial or full 5-HTIA agonists gepirone, zalospirone, and ipsapirone, have been studied. These molecules show anxiolytic properties but have limitations in terms of tolerability. In a recent brief report, Mathew *et al*. tested the short-term tolerability and efficacy of PRX-00023, a nonazapirone 5-HTIA selective partial agonist, in 23 outpatients with GAD (Mathew et al., 2008). This preliminary study indicated that PRX-00023 appeared to be generally well tolerated in patients with GAD. But further investigations needed.

2.1.5.2. Riluzole

Although double-blind, placebo-controlled trials are lacking, several open label trials have suggested that riluzole, either as monotherapy or as augmentation of standard therapy, reduces symptoms of some psychiatric disorders including generalized anxiety disorder (Grant et al., 2007; Mathew et al., 2005).

Mathew *et al*.,investigated the efficacy and safety of treatment with riluzole (100 mg/day): of the 15 patients who completed the trial, 12 had a rapid improvement of anxiety symptomatology (Mathew et al., 2005). Recently, Mathew *et al*. (2008), in an open-label trial, used proton magnetic resonance spectroscopic imaging (1H MRSI) to examine the effects of the glutamate-release inhibitor riluzole on hippocampal N-acetylaspartate (NAA), a neuronal marker, in 14 patients with GAD. Investigators demonstrated a relationship between hippocampal NAA and symptom alleviation after the administration of riluzole in patients for 8 weeks; this result suggested that riluzole might be efficacious for GAD (and subtypes of mood disorders) in part because of reduced glutamate excitotoxicity and enhancement of hippocampal neuroplasticity. In studies of psychiatrically ill patients conducted to date, the drug has been quite well tolerated; common adverse effects include nausea and sedation. Elevation of liver function tests is common and necessitates periodic monitoring. Riluzole may hold promise for the treatment of several psychiatric conditions, possibly through its ability to modulate pathologically dysregulated glutamate levels, and merits further investigation (Pittenger et al., 2008).

2.2. Nonpharmacological strategies; Psychotherapy

2.2.1. Cognitive behavioral therapy

One of the most successful psychosocial treatments for the treatment of GAD is cognitive-behavioral therapy (CBT). The components of this therapy may vary to include the following: education about the symptoms and causes of anxiety, cognitive restructuring, applied relaxation, increasing awareness, learning to monitor of anxious symptoms presenting as physical symptoms, and the automatic thoughts of worry created from situational and behavioral cues. Patients are taught to manage these symptoms through training in arousal reduction techniques such as pleasant imagery and diaphragmatic breathing; and imaginal and in vivo exposure to anxiety cues coupled with copings skill rehearsal (Roemer et al; 2002).

A Cochrane collaboration review concluded that current evidence demonstrates that CBT is effective for the short-term management of GAD relative to wait-list control but not active supportive therapy or supportive treatment (ie, active supportive therapies underpinned by humanistic principals). The most successful CBT treatment protocols have included motivational therapy, interpersonal psychotherapy, integrative CBT (ICBT) to treat GAD (Baer, 2003). Although CBT is the most effective of the psychological treatments available for GAD, available data indicate that a clinical response occurs in less than 50% of people receiving CBT, so unmet needs still remain (Hunot et al., 2007).

One promising form of psychotherapy emphasizes the promotion of positive emotional states and active coping behaviors, rather than focusing on how to reduce symptoms. This

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resilience-building treatment is referred to as "well-being therapy" and appears to be superior to CBT on some measures in treatment-resistant GAD and other forms of anxiety (Fava et al., 2005).

2.2.2. Mindfulness based cognitive therapy

A number of approaches have integrated features of Buddhist mindfulness practices with CBT to treat a number of psychiatric disorders including GAD (Baer 2003). Mindfulness was conceptualized as being a set of skills that can be learned independently of any spiritual or cultural tradition and then applied to help manage psychiatric symptoms. These approaches have included mindfulness based stress reduction (MBSR) (Kabat-Zinn 1982, 2003), mindfulness based cognitive therapy (MBCT) (Segal et al. 2002), dialectical behavior therapy (DBT) for borderline personality disorders (Linehan 1993a, b), and acceptance and commitment therapy (ACT) mostly for anxiety and major mood disorders (Hayes et al. 1999).

There are two objectives associated with classical mindfulness (CM) skill training for treating GAD: (1) to achieve a level of sustained, detailed, non-conceptual divided attention and awareness (also known as bare attention or direct experience), and (2) develop the ability to carry out experiential based insight based on the way of experiencing as described in (1). These two objectives clearly imply that there are two major stages of mindfulness practice. The first stage is training in sustaining, detailed, nonconceptual divided attention and awareness which needs to be distinguished as significantly different from MBSR practice of mindfulness. The second stage involves the reinstatement of gradual application of discriminative processes informed by direct experience in order to enrich the process of knowing (Rapgay et al., 2011).

MBCT may be an acceptable and potentially effective treatment for reducing anxiety and mood symptoms and increasing awareness of everyday experiences in patients with GAD. Future directions include development of a randomized clinical trial of MBCT for GAD (Evans et al., 2008).

2.3. Combination strategies

CBT in combination with a sub-therapeutic dose of diazepam produces a greater effect than the same dose of diazepam alone (Power, et al., 1989). Given that GAD has a chronic course and is often comorbid with depression it may be that the combined treatment of medication and psychotherapy may provide an important treatment option that could lead to improved outcomes beyond monotherapy (Barlow, 2002). Unfortunately, at this time there is no data to support this conclusion.

3. Conclusion

GAD is a prevalent and disabling disorder that may appear with physical and psychiatric comorbitidies. SSRIs and SNRIs defined as first line treatment options in GAD, and there is

increasing interest in enhancement new strategies to deal with the disorder. Novel antidepressants agomelatine and bupropion, atypical antipsychotics and anticonvulsants are promising in the treatment of GAD but still far from expectations because the necessity of close monitoring and some adverse events. Pharmacological interventions are still the most effective interventions to manage the disorder while augmentation strategies promising. However clinicians still in need of more effective treatment options that have rapid effect and safe.

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Chapter 14

Using Hypnosis in the Treatment of Anxiety Disorders: Pros and Cons

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Additional information is available at the end of the chapter

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1. Introduction

In psychotherapy outcome research, many empirical studies have shown that cognitive behavioural treatments are efficacious for many disorders [1]. In a recent systematic review of 27 studies, Hofmann and Smits [2] show that cognitive behavioural therapy (CBT) has proven to be an unquestionably efficacious treatment for adult anxiety disorder when compared to both pharmacological and psychological placebos. However, they conclude that there was considerable room for improvement. Moreover, the high complexity and co-morbidity that is often found with anxiety disorders sometimes requires the use of two or more treatment methods that are flexible and adjustable to one other [3]. According to Kirsch, Lynn, and Rue [4] and Schoenberger [5], hypnosis can be integrated easily into current cognitive and behavioural interventions in clinical practice. Indeed, CBT and hypnosis share a number of aspects that render their combination natural; for example, imagery and relaxation, which are found in both techniques [6]. Hypnosis has been used effectively in a variety of medical settings (surgery, dentistry, chronic pain management, labour etc.) and several studies report its efficacy in the treatment of anxiety disorders [7-13]. A recent systematic review of randomized controlled trials concludes that current evidence is not sufficient to support the use of hypnosis as a sole treatment for anxiety [14]. However, in a meta-analysis, Kirsch, Montgomery, and Sapirstein [15] found that the addition of hypnosis to CBT substantially enhanced the treatment outcome for several problems (anxiety, obesity, pain, etc.). The addition of hypnosis to CBT helps the patient in several aspects of therapy, such as the preparation for in-vivo exposure, imagery exposure, developing coping skills, and cognitive restructuring [6, 16-18]. Moreover, patients using hypnosis effectively develop a better sense of self-efficacy, which is known to enhance self-regulation and is linked to lower psychologi-

cal distress and better quality of life. Hence, hypnosis is worth exploring as an additional tool to improve traditional CBT.

In this chapter, we offer a comprehensive review of the literature regarding the use of hypnosis in the treatment of anxiety disorders. We will present evidence that supports its use or not as an adjunct treatment to CBT, also known as cognitive-behavioral hypnotherapy (CBH). We will also present evidence that does not justify its use as an independent treatment for anxiety disorders. Due to the amount of research on Post-Traumatic Stress Disorder (PTSD) and hypnosis, the reader will notice that a lot of the information will be related to PTSD. We will conclude by giving a simple guideline for practitioners interested in developing and using hypnosis as an adjunctive therapeutic tool in their practice.

2. Description and definition

Although under different names and applications, hypnosis has been depicted, described and documented in ancient civilizations (e.g. Egyptians, Greeks, Chinese, Indians, Sumerians, Persians and others) and was mostly used by healers. In his book *Ash Shifa* (Healing), Ibn Sina (Avecenna) wrote about the mind–body relationship and accepted the reality of hypnosis, naming it "al Wahm al-Amil" [19]. He differentiated it from sleep and described the impact of imagination on sensation and perception [20]. More recently, the British physician James Braid [1795-1960], who is recognized for conducting many research studies and experiments on hypnotic phenomena, coined the words *neurypnology and neuro-hypnosis* [21, 22]. In fact, he observed his patients while in trance and concluded that they were in a "nervous sleep." The Greek word for sleep is hypnos [21]. These terms were quickly transformed into the word *hypnosis*. Hypnosis lost its appeal with the rise of psychoanalysis during the first half of the 20th century [23]. Indeed, after a short interest in the practice of hypnosis, Freud abandoned and rejected the idea [21]. As a valid form of psychotherapy, hypnotherapy only regained its popularity with the advent of the First and Second World Wars [23]. During this time, psychiatrists were faced with a new disease, called *shell shock or war fatigue,* and used hypnosis as a way to relieve the symptoms [21]. Today, this disorder is known as PTSD. Subsequently, the modern study of hypnosis began to flourish. Throughout the years, hypnosis has been represented in various ways, whether good or bad, and many popular misconceptions around this phenomenon remain [22]. Indeed, people under hypnosis are sometimes viewed as robots who do things that they would not normally do [22]. Even though individuals under hypnosis are more prone to suggestions, they still remain in control of what they say and do [24]. In fact, despite the perception that experiences under hypnosis often contain automatic or involuntary actions, hypnotised patients ultimately act in congruity with their goals and in accordance with their points of view [25]. Another mistaken belief is that hypnosis is not real. However, recent scientific studies (e.g. brain imaging studies) go beyond these mainstream conceptions and expose the true nature of hypnosis and its possible uses [25].

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Burrows, Stanley, and Bloom [26] describe hypnosis as a technique that induces, through relaxed and focused attention, an elevated state of suggestibility. During this state, reduction in critical thinking, reality testing and tolerance of reality distortion allow the person to experience different phenomena (vivid imagery, drug free anaesthesia, drug free analgesia, and so on) that might otherwise be hard to attain [26]. Contrary to common perceptions, hypnosis is a natural phenomenon which people experience in a lighter way several times a day [27]. Daydreaming, being so absorbed by a book or movie that you do not hear someone calling your name or absent-mindedly driving past an expressway exit are all examples of shallow hypnotic states [27]. According to the division 30 of the American Psychological Association (APA), a procedure becomes a hypnotic one when the following two components are present: an introduction in which a person is told that suggestions for imaginative experiences will come, and the first suggestion, which functions as the induction [22]. Examples of suggestions during the introduction include: "I am going to ask you to imagine some changes in the way you think and feel. Is that ok? Let's see what happens" [22]. The formulation of hypnotic suggestions is different from other types of suggestions (e.g. placebo, social influence), given the fact that it requests the patient to participate [22].The first suggestion might come directly after the introduction and is usually a suggestion to close the eyes, move the arm or hand or alter perception [22]. Given that there are many types of hypnotic suggestions, standardized scales of suggestibility can be applied before someone undergoes formal hypnotherapy to see how suggestible the person is to all kinds of hypnotic suggestions [28]. During ideomotor suggestions, a certain action, such as arm levitation occurs automatically without awareness of volitional effort by the person [28]. Challenge suggestions occur when the hypnotised person is unable to execute an act that is ordinarily under voluntary control such as bending an arm [28]. Cognitive suggestions also can be used to create various cognitive or visual distortions such as pain reduction, selective amnesia, and hallucinations [28]. These different types of suggestions were characterized by Hilgard [29] as the domain of hypnosis.

Hypnotic experiences take place in the realm of imagination of the person under hypnosis [30]. However, it is interesting to note that hypnotic mental imageries and ordinary ones do not have the same experiential qualities [30]. Indeed, the construction of a mental imagery is both intentionally and consciously created, whereas imaginary experiences under hypnosis are generally involuntary [30]. People are suggested or informed about an image and it naturally comes to them. This difference seems to be supported by the fact that neurocognitive activations differ from normal and hypnotic imaginary experiences [31]. Another characteristic of hypnotic experiences, including the ideomotor ones, is that they are cognitive in nature [30]. Indeed, participants simply experience alterations in cognitive processes such as perception and memory. People differ in their abilities to experience hypnosis and it might be that some hypnotic responses require specific underlying abilities that are not shared by everyone, or that many individual components might be needed to experience a hypnotic phenomenon [32]. The ability to dissociate, cognitive flexibility, susceptibility to suggestions, fantasy proneness, and imaginative abilities were identified as possible traits that make an individual more amenable to experience hypnosis [33-36].

3. Theories of hypnosis

Hypnotic techniques became popular long before people knew what they were and how they worked. In the past, theorists viewed hypnosis as an altered state of consciousness or trance, but the quest to find evidence of this presumed state remained fruitless [28]. Indeed, it was discovered that people can respond in a similar yet slightly diminished way to non-hypnotic suggestions, suggesting that hypnosis is just another normal experience [28]. Moreover, since people under hypnosis are able to execute a full range of behaviours, theories needed to be able to encompass all of these aspects [28]. Due to the failure to explain such phenomena, several theories of hypnosis were developed, such as the psychoanalytic theory, the reality-testing theory, and more recently, the cold control theory and the discrepancy-attribution theory [21, 37, 38]. However, toward the end of the 20th century, two theories stood out as the most researched and influential ones: the dissociative theory and the sociocognitive theory.

Dissociative theories were first developed based on speculations about links between hypnosis and the phenomenon of dissociation [28]. Although a clear definition of dissociation is lacking, the first proponent of the dissociation theory described it as a split in the subunits of mental life, resulting in one or more parts left out from conscious awareness and voluntary control [39]. The neodissociative theory, developed by Hilgard, posits that hypnotic behaviours are produced by a "division of consciousness into two or more parts" [28] in which “part of the attentive effort and planning may continue without any awareness of it all” (p.2, 40]. Additionally, these subsystems are coordinated by a higher-order executive system, the 'executive ego' [39]. According to this theory, hypnosis alters the functioning of the executive ego, which tricks the mind about what is really going on. For example, when someone is asked to raise their arm under hypnosis, the executive ego might be responsible for the movement; however, because the awareness component of this has been separated into another part, this appears as an involuntary act to the hypnotised person [28].

Akin to dissociative theories, sociocognitive theories reject the idea that hypnosis requires an altered state of consciousness [41]. In fact, the same individualized social and cognitive variables that shape complex social behaviours are thought to determine hypnotic responses and experiences [41]. These variables are (a) a positive experience (attitudes, expectations, beliefs) with hypnosis in general, (b) good motivation to respond to suggestions, (c) clear indications that signal how to respond to hypnotic suggestions, and (d) implicit or explicit instructions in which to become absorbed or to imagine suggestions provided by the hypnotist. It is thought that when all of these variables are working together in a given individual, the person is under hypnosis [25]. Moreover, sociocognitive theories state that responses under hypnosis are goal-directed and that hypnotised people continue to act according to their aims and values, just as they ordinarily behave according to a socialized role [42]. Finally, rather than being attributed to an altered state of mind, the enhanced responses seen in people under hypnosis are merely a reflection of increased motivation and expectations [42].

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Beyond differences and resulting controversy steaming from the dissociative and sociocognitive theory perspectives, new findings from psychophysiological and brain imaging studies have allowed the scientific community to support the hypothesis that experiences under hypnosis are "genuine" [24]. Indeed, studies demonstrated that there are distinctive patterns of activation (anterior cingulate cortex and frontal cortical areas) attributable to hypnosis and that these patterns comprise mechanisms used in other familiar cognitive tasks (focused attention, imagination, absorption) [24, 31]. Furthermore, there are specific psychophysiological correlates for suggested experiences [24, 31]. Some studies demonstrated that there is a qualitative distinction between neurocognitive activations that occur when people are asked to imagine certain images under hypnosis and in ordinary conditions [31]. Also, the hypnotic experiences appear to create brain states closer to the real experience, a phenomenon corroborated by the subjective reports of individuals [31]. Finally, brain imaging and psychophysiological studies might also enrich our understanding of the respective contribution of the social context, the subject's aptitudes, expectations, and intrasubjective experience of hypnotic phenomena.

4. The clinical use of hypnosis

4.1. Medical conditions

4.1.1. Hypnosis alone

Thus far, the value of hypnosis has already been recognized for many physical and medical conditions. Indeed, in 1996, the National Institute of Health Technology Assessment Panel Report considered hypnosis as a viable and effective solution to treat pain associated with cancer and many other chronic pain conditions [43]. It was even found that in certain conditions, the degree of analgesia resulting from hypnosis matched or even exceeded that provided by morphine [43]. These findings are supported by the results of Montgomery, DuHamel, and Redd's[44] meta-analytic review, which found that 75% of the people experienced pain reduction due to hypnosis, and these reductions were found in both a clinical and a healthy population. In their review of the literature, Neron and Stephenson [45] also present evidence on the effectiveness of hypnotherapy for emesis, analgesia, and anxiolysis in acute pain. Montgomery et al. [46] found that when compared to empathic listening, presurgery hypnosis was more effective in reducing pain intensity and pain unpleasantness for breast cancer patients. In addition to reducing the pain associated with cancer, hypnosis was also found to effectively reduce the affective morbidities (anxiety, discomfort, and emotional upset) associated with the medical procedures [46-48], as well as reduce fatigue [46, 49], sleep problems [49], nausea [46] and the quantity of medication needed [46]. Similar results (reduction in pain, anxiety and medication and better satisfaction) were found for plastic surgery patients [50], severe burn care patients [51], women giving birth [52], breast biopsy patients [53] and patients undergoing dental procedures [54]. Hypnosis also served as a sole anaesthetic ingredient

for thousands of surgeries [43]. Other medical conditions that have been found to be responsive to hypnosis are preoperative preparations for surgery, a subgroup of patients with asthma, dermatological disorders, irritable bowel syndrome, hemophillia, post-chemotherapy nausea and emesis (Pinnell & Covino(2000) cited in 43). Of note is that in the medical environment, clinical hypnosis is provided as an adjunct to medical treatment. There is usually no time for multiple sessions based on skills acquisition and homework. Intervention is often provided at bedside, or in preparation and during medical procedures away from the usual office-based psychotherapy setting. The goal of care is often symptom relief and comfort during the medical procedure and not psychological therapeutic change, which is typically the end point of psychotherapy. Hypnosis is used because it is efficacious but most importantly it is practical (short: minimal practice, no homework or assignments; portable: self-hypnosis)[1].

4.1.2. CBH As an adjunct to CBT

Kirsch et al. [15] reported substantial effect sizes for problems such as weight loss, pain, anxiety, and insomnia. More specifically, it was found to be particularly effective for the treatment of obesity [15, 56]. Indeed, long-term weight loss was maintained at follow-ups, which is an issue for most people who gain their weight back soon after losing it [15]. In their review of the literature, Chambless and Ollendick [57] even identified hypnosis (in conjunction with CBT) as an empirically supported therapy for obesity, along with headaches and irritable bowel syndrome [57]. A study done with women suffering from chronic breast cancer pain revealed that cognitive hypnotherapy or CBH was effective not only in reducing pain, but also in decreasing pain over time as the cancer progressed [58]. As for cigarette smoking, many studies assessing the use of hypnosis as an adjunct to cognitive-behavioural interventions found good results [59], with the rate of abstinence varying from 31 to 91% at the end of treatment and 31 to 87% around the three-four month follow-ups [56]. However, these results should be interpreted with caution, as some research demonstrated considerable limitations such as the exclusive use of self-reports, small sample sizes, a lack of differentiation between hypnosis and relaxation techniques and no clear definition of cigarette smoking [56]. More recently, some studies using more reliable approaches showed promising results in the use of hypnosis for cigarette smoking. Indeed, results indicate that after treatment, at three month, six month and 12 month follow-ups, more participants in the hypnosis group were abstinent [60, 61]. Rather than using CBH, these studies either compared hypnosis to behavioural treatment or to a waiting-list control group. Hypnosis appears to be a promising avenue for many physiological and psychological problems but most importantly, hypnosis is a cost-effective alternative procedure [43]. However, as Schoenberger's review [62] indicates, more rigorous

1 Flory & Lang provide examples and data supporting this type of hypnotic intervention used as a flexible and practical tool to alleviate pain, anxiety, and treatment side effects while potentially reducing the need for sedation and stabilizing the vital signs [55].

methodologies as well as more studies comparing specifically the added benefit of hypnosis to CBT are needed to determine its real effects.

4.2. Anxiety disorders

4.2.1. Social anxiety disorder

The essential feature of social anxiety disorder (SAD) or social phobia is an important and persistent fear or worry about social and performance situations [63]. Social phobia can be divided into two types: generalized, in which individuals fear most social situations (e.g. having a conversation, facing authority, speaking in front of people and so on); and specific, when individuals only fear one particular situation (e.g. eating in front of people). According to different studies, the prevalence of SAD ranges from three to 13 % of the population. In their review of five meta-analyses that looked specifically at the treatment of SAD, Rodebaugh, Holaway, and Heimberg [64] found that CBT appears to provide benefits for adults diagnosed with SAD, with modest to large effect sizes when compared to waiting-list control, as well as moderate to large effect sizes from pre to post-treatment.

Hypnosis as a sole treatment. To our knowledge, there is only one randomized controlled trial testing the use of hypnosis as a sole treatment for social phobia. In early attempts to view the potential of hypnosis to treat social anxiety, Stanton [65] randomized 60 adults seeking help for handling their anxiety. Anxiety levels were assessed by the Willoughby Questionnaire. The author compared a hypnotic procedure consisting of positive suggestions and mental imagery to another group that listened to quiet music (movements from Mozart symphonies) and to a control group. Both experimental groups met in their respective groups for 30 minutes for three weeks. At the end of treatment, both experimental groups experienced a significant reduction in their anxiety, whereas the control group saw minor changes in their anxiety levels. Moreover, the reduction for the hypnosis group was larger. Finally, the therapeutic gains were maintained for the hypnosis group only at six month follow-ups. Although these results were encouraging, this study presented many limitations such as the fact that there was no statistical calculation of the difference between the hypnosis and music groups and that the validity of the instrument was not presented. One case report also indicated that hypnosis was useful in treating social phobia [66]. Although hypnosis was used as a sole treatment, the author pointed out that the patient had experience with typical phobia treatments such as systematic imaginal and in-vivo exposure and that this familiarity might have contributed to the successful outcome.

CBH. Schoenberger, Kirsch, Gearan, Montgomery, and Pastyrnak [67] conducted a randomized controlled study on public speaking anxiety in which they compared the efficacy of CBT to the same therapy combined with hypnosis and a waiting-list control group. The experimental treatments included cognitive restructuring and in-vivo exposure. The hypnosis component consisted of replacing relaxation training by hypnotic inductions and suggestions [67]. In terms of self-report measures of public speaking

anxiety, both experimental treatments produced a reduction in anxiety compared to the control group. As for the subjective and behavioural measures of fear, only the hypnotic group differed significantly from the control group. These measures were taken by a blind observer during a impromptu speech that participants gave in front of two observers. Finally, the mean effect sizes calculated across the dependant measures revealed a significant difference between the two experimental groups in favor of the hypnotic treatment (mean effect for the nonhypnotic treatment is 0.80 standard deviation and 1.25 standard deviation for the hypnotic treatment, $t(5) = 3.75$, $p < .05$) [67].

4.2.2. Specific phobias

A phobia is characterized by a marked and persistent fear prompted by the presence or anticipation of an encounter with a specific object or situation [63]. This situation can create a sensation of panic, somatic manifestations of anxiety, fainting or even trigger a panic attack in the phobic person. According to the DSM-IV-TR [63], there are 5 subtypes of phobias: animal type, natural environment type, situational type, blood-injection-injury type, and other type, which includes all phobias that do not fit in the previous categories. The lifetime prevalence rate varies from 7.2 to 11.3%. CBT procedures (including in vivo-exposure and systematic desensitization) are considered the treatments of choice for specific phobias [68]. Even though these techniques apply to most phobias, certain ones require specific adaptation such as the applied tension technique for blood-injury-injection phobias [68].

Hypnosis as a sole treatment. We found two randomized controlled studies that utilized hypnosis as a stand-alone treatment for specific phobias. In the first one, Hammarstrand, Berggren, and Hakeberg [69] compared a group of women with dental phobias using two types of experimental treatments: a behavioural treatment based on psychophysiological principles, and hypnotherapy. The psychophysiological treatment consisted of progressive relaxation, videos of dental scenes and biofeedback training. As for the hypnotherapy, the participants were told to imagine different dental scenes, which corresponded to the videos of the psychophysiological group, and received suggestions. In addition, a control group who received general anaesthesia was added. Unlike the rest of the participants, this group was not randomized. The results showed that only the psychophysiological group experienced a significant reduction in anxiety. However, no significant difference between the two experimental and control groups was found. It should be noted that out of the 22 participants in this study, only 13 completed the treatments (eight in the psychophysiological treatment, five in hypnotherapy) and thus the sample was too small to draw real conclusions. Moreover, since the control group was not randomized, there is the possibility that these participants were different from the other two groups. In an exploratory study of four people suffering from specific phobias (i.e. fear of flying, snakes, driving, and heights), Llobet [21] assessed the effectiveness of group hypnotherapy. The hypnotherapy consisted of imaginary exposure with the use of the "magic bubble technique "[2], as well as the age regression technique[3] [21]. The author

stated that behavioural techniques expose patients to the avoided stimuli in a "here and now" context [21]. Although these techniques have been proven efficacious, therapy should employ self-exploration in order for patients to understand their unique conscious and unconscious processes [21]. Age regression hypnotherapy can thus solve this problem [21]. Results of this study indicated that all participants saw their anxiety reduced in a significant way. Even though the participants' anxiety increased slightly at the two-week follow-up, participants still experienced on average a 56.46% decrease compared to their baseline score. The benefits of the group therapy might have been enhanced if it was combined with other well-recognized methods for treating phobias – a focus for future research.

CBH. As for the integration of hypnosis with CBT or behavioural protocols for specific phobias, we found several case reports and case studies and only one randomized controlled trial. Recently, Forbes [71] compared the relative effectiveness of systematic desensitization with hypnosis to the same treatment with relaxation in the management of animal phobias. His results showed that patients in the hypnosis group enjoyed greater anxiety reduction than the other group. Finally, case studies also corroborated the effectiveness of CBH for driving phobia [72], animal phobia [73], and airplane phobia [74]. This evidence tends to support the use of CBH as an effective therapy for different types of phobias.

4.2.3. Panic disorder with or without agoraphobia

The main feature of Panic Disorder with or without Agoraphobia (PD/A) is the presence of recurrent, unexpected panic attacks, accompanied by persistent concerns about having other panic attacks, worry about the possible implications or consequences of panic attacks, or a significant behavioural change related to the attacks [63]. As for panic attacks, they are discrete periods of intense fear or discomfort that are accompanied by both physical and cognitive symptoms such as heart palpitations, hyperventilation, dizziness, a fear of losing control or going crazy, depersonalization and so on. People who suffer from PD sometimes develop agoraphobia, which is an anxiety related to being in places or situations in which escape might be difficult or impossible and help difficult to receive. In community samples, rates vary between one and two percent, although higher rates [3.5%) were found in some studies (75]. When treating PDA, both the Canadian Psychological Association (CPA) and the APA recognize CBT as the first line of treatment [76]. Indeed, efficacious and robust treatment effects of this therapy have been verified across a variety of treatment settings for extended follow-up periods.

Hypnosis as a sole treatment or in conjunction with other non- cognitive and behavioural techniques. The use of hypnotic techniques to treat PD/A was successfully identified in some case reports [77-79]. Hypnotic techniques such as age regression, hypnoanalysis[4] [77], ego-strength-

2 In order to render exposures less distressing, patients under hypnosis are suggested to imagine themselves in a magic bubble when they revisit their feared object or situation, which acts as a protection.

3 During age regression, the person is guided back in time to a past experience in order to relive it, or the person can also be suggested to remember the experience in a here-and-now as vividly as possible [70].

ening suggestions [78], and the use of medication in conjunction in one case [79] led most patients to become panic free. However, no controlled trial studies could be found on hypnosis alone.

CBH. In the only controlled trial study on the efficacy of CBH in treating PDA, Dyck and Spinhoven [80] demonstrated that a combined therapy (self-hypnosis and exposure) was not superior to exposure alone in terms of time spent by agoraphobics walking on a prescribed route. In this case, the hypnotic technique employed was imaginary exposure plus suggestions from the therapist consisting of successful encounters with the feared situation (prescribed route). One problem with this study is that it used a cross-over design (exposure alone and then combined/ combined followed by exposure alone) and thus the eventuality that patients still continued to use hypnosis during the exposures alone cannot be ruled out. Thus, reservations must be kept in mind with regard to these latter results. Interestingly, the authors also found that preference for treatment shifted toward the combined treatment as the study went on [80]. Positive results for CBH were demonstrated in many case reports [18, 81, 82]. Indeed, hypnosis was found to enhance CBT protocols by facilitating exposures to both the symptoms of panic and situational anxiety. Moreover, it also was found to be successful in conjunction with Rational Emotive therapy (RE).

4.2.4. Generalized anxiety disorder

People who suffer from Generalized Anxiety Disorder (GAD) experience excessive and hardly controllable worry and anxiety most of the time. Contrary to some other anxiety disorders where the anxiety is focused on a specific event or thing (e.g. specific phobia), GAD individuals worry about different situations and activities. Many individuals also develop somatic symptoms such as muscle tension, nausea, and sweating. In community samples, approximately three percent of the population will develop GAD [63]. As for the treatment of GAD, traditional narrative reviews and meta-analyses have consistently found that CBT and applied relaxation are the most efficacious treatments [83].

Hypnosis as a sole treatment. Recently, a study investigated hypnosis as an alternative method for CBT in the treatment of GAD [27]. The hypnosis component was comprised of suggestions involving the lessening of anxiety. Based on the Beck Anxiety Inventory (BAI) scores of 60 patients, the author stated that there was evidence of hypnosis being as effective as CBT in the treatment of GAD [27]. These results were derived from the archived records of a local licensed mental health therapist's private practice. Although these results are positive, the patients were not randomized to the treatments but rather assigned to treatment based on their own desire to receive hypnotherapy or CBT. It is thus safer to say that hypnosis was as effective as CBT for patients who believed in and wished to be treated with hypnotherapy. Also, since this was a retrospective study, many aspects such as the number of sessions, and the integrity of therapy could not be controlled for.

4 Hypnoanalysis is a mix of hypnosis and psychoanalytic techniques

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CBH. In a pilot randomized controlled study of 10 patients, Allen [84] assessed the comparable efficacy of a treatment incorporating CBT, hypnosis, and biofeedback to a waiting-list control group. All patients in the experimental group demonstrated a reduction in both trait and state anxiety. Most of them (four out of five) even obtained post-test state anxiety scores below the normative range. As for the control group, their anxiety remained at a clinically significant level [84]. CBH also came out as a successful aid in the treatment of GAD, as demonstrated by Baker's [85] case report.

4.2.5. Obsessive-compulsive disorder

Obsessive-Compulsive Disorder's (OCD) main features are recurrent obsessions and/or compulsions that are so severe that they are time-consuming and/or cause distress to the person. Obsessions may be persistent ideas, thoughts, impulses or images that can be related to many different topics such as contamination, religion, symmetry and repeated doubts. As for compulsions, they are repetitive behaviours or mental acts that people perform in order to diminish the anxiety associated with their obsessions. The estimated lifetime prevalence of OCD is 2.5% [63]. In a recent review of the literature, Podea, Suciu, Suciu, and Ardelean [86] concluded that CBT is an effective treatment for OCD, that it is at least as effective as medication and that it demonstrates good benefits at follow-ups.

CBH. So far, hypnosis has occupied a relatively restricted role in the treatment of OCD [87] and this is reflected in the few numbers of studies on this topic. Indeed, no well controlled studies on the efficacy of CBH have been completed so far to see the additive effect of hypnosis to CBT [88]. Rather, the hypnosis literature only contains descriptions of clinical work done with a minimal number of patients and a series of case studies usually unaccompanied by measurable data. Still, as a combination to CBT, hypnosis was found to be efficacious in many case reports and one case study [88-92]. For example, because his patient did not respond to CBT and medication, Frederick [88] developed an intervention in which CBT and hypnoanalysis were incorporated. The hypnosis part was mainly aimed at the resolution of the dissociative symptoms. Other authors used hypnosis during exposures (e.g. exposure-response prevention, flooding) in order to enhance its effect, relieve anxiety and ameliorate the patients' affect regulation [90-92]. Very recently, Meyerson and Konichezky [87] presented three single-case reports in which hypnotically-induced dissociation (HID) combined with CBT protocols was successfully used in order to treat patients with OCD. According to Yapko [93], HID is the ability to split a fully and unified experience into many different components, while amplifying awareness of one part and diminishing awareness of the others. For example, some patients report that they cannot recognize themselves without their disorder. HID can thus be used to help the person dissociate him or herself from the disorder and amplify their feeling of experiencing life without the disorder.

4.2.6. Post-traumatic stress disorder

In the DSM-IV-TR [63], PTSD is described as the development of characteristic symptoms after an individual is exposed to an extreme traumatic stressor (A1). The traumatic event must put at risk the physical integrity of the individual or others and the person's response must involve intense fear, helplessness, or horror (A2). The characteristic symptoms of PTSD include (B) stress and hyperarousal, (C) persistent avoidance of situations or reminders of the trauma and (D) vivid experiences of being back in the midst of the traumatic event, which are often referred to as a *flashback.* Finally, (E) these symptoms must last for at least one month. If the time is less than that, the diagnostic is labelled as Acute Stress Disorder (ASD). PTSD lifetime prevalence rates are approximately eight percent. In high risk populations such as veterans, these rates may rise to as high as 30% [94]. In terms of treatment, variations of CBT protocols such as cognitive processing therapy (CPT) and prolonged exposure are known to effectively treat PTSD symptoms [95].

Among all of the anxiety disorders, the addition of hypnosis to CBT in the treatment of PTSD is the most studied. This interest has been triggered by factors such as the evidence that PTSD patients seem to be more highly hypnotisable when compared to the general population and other patient populations [96-98]. Butler, Duran, Jasiukaitis, Koopman et al. [99] developed a diathesis-stress model of dissociation to explain this phenomenon which is that "highly hypnotisable/dissociative people would be more likely to develop posttraumatic/ dissociative conditions rather than other psychiatric conditions". Evidence in support of this model are the fact that higher scores on hypnotisability scales are associated with avoidance symptoms, which is a core aspect of PTSD [96] as well as with better therapeutic success [100]. However, research is needed to exclude the possibility that it is the development and maintenance of PTSD that create a state of high hypnotisability. Moreover, clinical findings seem to suggest that there is a similarity in phenomenology between PTSD symptoms and the experience of hypnosis [101]. For example, during hypnosis, the person is entirely focused and absorbed into the suggestions and this absorption is also evidenced in PTSD sufferers, who sometimes focus so intensely on their traumatic memories that they are able to create physical and emotional responses. Another common factor is the phenomenon of dissociation, which can occur both during and after the trauma. Finally, both PTSD and hypnosis are experiences in which the person is hyper-responsive to both their environment (social, physical cues) and internal cues [101]. Because traditional interventions are mostly aimed at targeting the core symptoms of PTSD, the interest in hypnosis was also prompted by the fact that as a flexible form of treatment, it might be able to target important symptoms such as sleep and dream disturbance, pain, and emotional and anxiety withdrawal problems associated with traumas [100, 102].

Hypnosis as a sole treatment or in conjunction with relaxation training. A recent randomized controlled study tested the hypothesis that hypnosis could help relieve the cluster of hyperarousal symptoms in PTSD, in a group of women who had experienced sexual trauma [103]. This study compared the use of a hypnotic induction (Elkins Hypnotisability Scale) to a standard care intervention, which was a combination of supportive counselling, CBT, interpersonal therapy, and solution-focused technique [103]. Following the ini-

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tial induction, a hypnotic induction recording for subjects in the treatment group was given to use at home over a period of one week. The author reported a statistically significant decrease in hyperarousal symptoms, general anxiety, and difficulty concentrating for the hypnotic group [103]. However, participants did not fall under the clinically significant line, and on many measures there was no significant difference between the control and treatment group. Some noticeable limitations of this study were that even though the groups were randomized, some of the baseline symptoms of the hypnosis group were more severe than that of the control group, which might explain the small differences between the two groups on some measures at the end of treatment. [103]. Even though it was the study's goal to create a short treatment, it came out that one week was probably too short of an interval to see the real effects of hypnosis and reach clinically significant results. It would have been interesting to see the added benefit of hypnosis to the standard treatment over a longer period of time. Moreover, in this study, there was minimal use of hypnosis. Indeed, the hypnotic induction did not include any suggestions to treat aspects of PTSD.

As part of their symptoms, PTSD sufferers often complain about sleep problems [17]. Some studies indicated that hypnosis can be helpful in reducing time to sleep onset in a group of individuals with chronic insomnia [104, 105]. A meta-analysis of 59 outcome studies also demonstrated that the short-term effects of hypnosis (one-two months) and relaxation training were comparable to the effects of short-term drug therapy and that the long-term outcomes even surpassed the drug therapy in certain instances [106]. Abramowitz, Barak, Ben-Avi, and Knobler [107] studied a group of chronic combat-related PTSD sufferers who experienced sleep problems even though they received supportive therapy and serotonin reuptake inhibitors (SSRIs). The participants had difficulty falling asleep as well as maintaining sleep and reported night terrors. The authors compared the efficacy of two weeks of one-and-a-half hour hypnotherapy sessions with the drug therapy Zolpidem to see the effects on PTSD symptoms and sleep problems. They found that in addition to see a reduction in the major PTSD symptoms, the hypnotic group reported better sleep quality, fewer awakenings, and less morning sleepiness.

CBH. There are many recent instances of case studies and reports that describe the success of hypnosis in conjunction with CBT for traumas associated with industrial accidents [108-110], motor-vehicle accident [111], sexual abuse and rape trauma [112-114], spouse abuse-related trauma [101, 114-116] and assault-related trauma [117]. For example, Degun-Mather [118] [119] reported the success of hypnosis in conjunction with CBT in two cases of patients suffering from different traumas (childhood and war). Hypnotherapy was used in order to activate and reconstruct the traumatic memories. On a larger scale, Brom, Kleber, and Defares [120] compared the effectiveness of four psychotherapeutic methods for the treatment of PTSD in 112 patients: hypnotherapy based on behavioural techniques, trauma desensitization, psychodynamic treatment, and a waiting-list control group, and determined that the treatment groups were significantly lower in trauma-related symptoms than the control group. However, the authors of the original study reported that there was still a lot of similarity between the three treatment conditions which could be due to similarities in the be-

haviours of the therapists, which they did not measure directly. No statistical measures were presented to compare the active treatment groups. In their systematic review, Coelho, Canter, and Ernst [14] reanalyzed the data and found that on some measures (STAI-S, STAI-T, IES), the hypnotic group obtained statistically better results compared to the other treatment groups both at post-test and follow-up. Bryant et al.'s [121] randomized study compared the effectiveness of CBT, hypnosis and CBT, and social counselling for trauma survivors who suffer from ASD. The rationale behind their study was that hypnotic techniques might be able to breach dissociative symptoms of ASD [121]. A hypnotic induction was thus given right before imaginal exposure, in an attempt to ease the emotional processing of the traumatic memories [121]. Their results indicated that at post-treatment and follow-ups (six months, three years), fewer patients in the CBT (2.11%) and hypnosis with CBT group (4.22%[5]) met criteria for PTSD [121]. Also, hypnosis with CBT resulted in fewer re-experiencing symptoms than CBT alone at post-treatment, but this difference was not found at follow-up [121]. Even though these results are positive, the authors used hypnosis in only one aspect of their therapy (imaginary exposure). Hypnosis has many functions and is exploitable in many parts of therapy (which will be described in details below) and thus a broader application of it might have generated more additive gains and yielded clearer results. Moreover, the literature on hypnosis and PTSD is filled with examples of how hypnosis can be used specifically in the treatment of PTSD, so that its benefits can be enhanced. For further reading, see Lynn et al. [17] and Degun-Mather [119].

Recently, a new hypnotic technique called hypnotherapeutic olfactory conditioning (HOC) showed promising potential in the treatment of PTSD. Based on CBT protocols, HOC is a technique that helps patients create new olfactory associations in order to surmount anxieties and dissociative states [102]. More precisely, it is the "development, under hypnosis, of a positive olfactory association which allows the patient to regain control of their symptoms, especially when they were created by olfactory stimuli" (p.317 102). This technique is based on the notion that the sense of smell has the ability to create vivid memories due to the particular position of the olfactory bulb in the brain [102]. In an exploratory study of three individuals suffering from needle phobia, panic disorder and PTSD respectively, Abramowitz and Lichtenberg [122] found a marked reduction in the symptoms, as attested by the rating scales and reduction in the use of medication. In a prospective study testing HOC with 36 patients suffering from chronic PTSD, results demonstrated significant reductions in symptoms, as assessed by the Impact of Events Scale (IES–R), Beck Depression Inventory, and Dissociative Experiences Scale [102]. The gains were maintained at six month and one year follow-ups. In this study, the authors did not compare the direct added benefits of HOC to standard protocols. However, the fact that most patients had already been in therapy for a mean time of more than two years and that baseline symptoms presented significant psychopathology indicates that HOC was able to provide additional benefits to the therapy. Still, replication studies are needed for HOC.

5 results for 3 year follow-up.

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4.2.7. Other anxiety-related problems

Hypnosis as a sole treatment. A 1978 study looked at the difference between two non-pharmacological interventions in the treatment of what was then called "anxiety neurosis". The two treatments were either a meditational relaxation technique comprised of muscle relaxation and concentration on inner breathing and stillness, or a self-hypnosis treatment, also comprised of muscle relaxation and suggestions to send tingling feelings and light to the parts of the body where anxiety symptoms were manifested [123].The participants were tested on levels of hypnotisability and were then separated into two groups: medium-high hypnotisable subjects and low hypnotisable subjects. Then, the participants in each group were randomized to one of the two experimental treatments. Although more participants in the hypnotic group improved according to the Hamilton Anxiety Rating Scale, the results indicated that there was essentially no difference between the two techniques in terms of therapeutic efficacy [123]. However, participants in the medium-high group, independently of the type of treatment, significantly improved on the psychiatric assessment and demonstrated a decrease in their average systolic blood pressure [123]. One major limitation of this study is that at the beginning, the authors randomized 69 people to the four treatment conditions, however, 37 of them did not complete the protocol. Thus, in addition to providing no results on the drop-outs, the benefits of randomization cannot be assumed in this study. Moreover, the hypnosis treatment was very similar in content to the meditational group, which can explain the minute difference between the two. Stanton [124] randomly assigned a group of 40 students to either a self-hypnosis training group or a control group, which consisted of discussions on ways to reduce test anxiety. The participants were matched on sex and anxiety scores. After two sessions and at a six month follow-up, anxiety scores were significantly reduced for the hypnotic group only. More recently, O'Neill, Barnier, and McConkey [125] compared self-hypnosis training with progressive relaxation in a group of stressed, anxious, and worried patients. At a one month follow-up, both groups indicated significant improvement on the Beck Anxiety Inventory (BAI-State and Trait) but no significant difference was found between these two groups on the BAI. However, the hypnosis group surpassed the relaxation group on cognitive changes and perceptions of treatment efficacy [125]. Indeed, the hypnosis patients reported superior expectations of the success of therapy [125]. A closer look at the procedures revealed that the content of the instructions given to both groups were very similar. These results seem to indicate that the simple fact of defining certain aspects of therapy *hypnosis* provided confidence and better expectation in patients [16]. Finally, in an attempt to determine the effectiveness of hypnosis on test anxiety, Hyman [126] randomized 21 participants to a hypnotic-induction only group, a post-suggestion hypnotic group or a control group. The participants received only one session of hypnosis and the post-hypnotic suggestions consisted of suggestions for reduction of test anxiety [126]. The results showed that directly after the inductions, there was no significant difference between the three groups, as evidenced by the Test Anxiety Inventory (TAI). At one month follow-up though, a significant difference was observed between the post-hypnotic group and the control group in terms of anxiety. The post-hypnotic suggestion group was also the only group who experienced a significant decrease in test anxiety over time (between post and follow-up assessments). Although the sample size of this study was very

small, this seems to indicate that post-hypnotic suggestions might be one of the active ingredients of hypnosis *CBH.*

A study comparing the effects of two hypnotic procedures (imagery and cognitive restructuring under hypnosis versus hypnotic induction only) with two control groups (attention placebo and no treatment) on the treatment of test anxiety supports the idea that the combination of hypnosis and CBT offers more therapeutic gains [127]. Indeed, results indicate that while the induction-only group had more improvements than the two control groups, only the group receiving imagery and cognitive restructuring under hypnosis obtained significant results on anxiety and academic performance [127].

4.2.8. Summary and conclusions on the clinical use of hypnosis

To date, except for PTSD, there is a very small number of randomized controlled studies assessing the impact of CBH for the treatment of anxiety disorders, which limits the conclusions that can be drawn about its external validity. However, the results presented above still indicate that CBH is a promising treatment modality. Indeed, in addition to demonstrating its efficacy as a complete intervention to reduce anxiety symptoms, all studies that compared the additive effect of hypnosis found positive results, except for one. As stated before, this study used a cross-over design which might explain the lack of superiority for the combined group (exposure and hypnosis). Also, Mellinger [128] and Scrignar [91] reported the success of hypnosis as a valuable adjunct to render exposure practices more viable. Finally, using non-leading methods, Degun-Mather [118] reported the successful use of hypnosis to transform the fragmented memories of a war veteran who suffered from chronic PTSD and dissociative fugues into a complete narrative, leading to re-appraisal and re-structuring of the trauma. As for the evidence supporting hypnosis as a stand-alone treatment, results are mixed. Indeed, some of the case reports and studies presented above found positive results [21, 27]. On the other hand, in 2003, the STEER [129] looked at four randomized controlled trials of hypnotherapy as a sole therapy for anxiety, coming to the conclusion that there was insufficient evidence regarding the efficacy of hypnotherapy and that it did not appear to be more effective than other treatments. In their conclusion, the authors of the STEER report also mentioned that the general quality of all studies was unsatisfactory. All of them presented major methodological flaws, such as a lack of established questionnaires, no use of imagery or suggestions during hypnosis, small sample sizes and no clear indications of qualification of competence of the therapists. This again renders it difficult to draw firm conclusions. More recently, a systematic review of controlled trial studies revealed that hypnosis as a sole treatment for anxiety was not superior than control conditions (waiting list controls, contact controls, or other non-standard treatments) [14], and though it is a powerful supportive tool, using it as a therapy by itself is an error [130]. Research on clinical hypnosis should reflect the clinical practice in psychotherapy, [56] and thus hypnosis should be viewed and studied as an adjunct to commonly used and recognized techniques. In fact, hypnotic technique can directly reinforce CBT strategies by helping patients to control and regulate the anxiety as well as the cognitive and attentional processes characteristic of many

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Disorders	Hypnosis alone	CBH
Social anxiety disorder	Good outcomes [65-66]	Good outcomes [67]
	Significant reduction in anxiety at post-test and superiority of hypnosis at six-month follow-ups [66]	CBH more efficacious than CBT alone
Specific phobias	Mixed results [21][69]	CBH and HOC as an effective treatment [71-74]
	Significance was reached in the Llobet study [21] but not in the Stanton study [69]	CBH provided better results than CBT alone [71] HOC allowed patient to face the phobic situation with success [122]
Panic disorder with or without agoraphobia	Generally good results [77-79]	Mixed results [18][80-82][122]
	Only based on case studies and reports. Intensity of episodes is reduced while other patients are panic-free	No superiority of CBH compared to CBT in one study, but patients received both treatments in a cross-over design, which limits the conclusions [80] Effective relief of symptoms found in other studies [18][81-82][122]
Generalized anxiety disorder	Good outcomes [29]	Good outcomes [84-85]
	Hypnosis as effective as CBT (no randomization)	Most patients in hypnosis and CBT group obtained anxiety scores below the normative ranges at post-test [84]
Obsessive-compulsive disorder	Not applicable	Good results [88-92]
		Based on case reports
Post traumatic stress disorder	Good outcomes [103-107]	Good outcomes [102][108-122]
	Statistically significant reduction in hyperarousal symptoms but results did not reach clinical significance [103] Hypnosis effective for treating sleep problems [104-105] and equivalent or better than drugs [106-107]	CBH superior to CBT and other techniques on some measures [120-121] HOC found to be effective in reducing symptoms at post-test [102][122] and six-month follow-ups [102]
Other anxiety-related problems	Mixed results [123-126]	Good outcome [127]
	Improvement but no indication that hypnosis as a sole treatment is more efficacious than other methods or no treatment, except for one study [124]. Superiority only stood out at one-month follow-up in another study [126]	Superiority of CBH over hypnosis alone and control groups

Table 1.

anxiety disorders [87]. One point to note, however, is that the boundaries between hypnosis as a stand-alone treatment and as an adjunct are sometimes unclear, as some people view a hypnotic induction followed by suggestions as CBT in itself [14]. For a summary table of the data presented above, see table 1.

5. Guidelines and benefits of the application of hypnosis to CBT protocols

5.1. How to integrate hypnosis to CBT components

As a psychosocial treatment, CBT has roots in both the cognitive and behavioural traditions and is based on the idea that our thoughts influence our feelings and behaviours [131]. Important components of CBT include relaxation training, exposure (both imaginal and in-vivo), cognitive restructuring, the building of coping skills, ego-strengthening, and self-efficacy. In the following, based on what several authors described (William, Bryant, Lynn and colleagues, Alladin, Degun-Mather), we will report a summary of how hypnosis can enhance each of these components [6, 16, 17, 23, 119]

Developing a good therapeutic alliance and motivation toward the therapy. The benefits of adding hypnosis to standard treatments of anxiety are manifold. The basis of therapy is the development of a good therapeutic alliance. The goal-directed and generally positive environment surrounding hypnosis may promote a better rapport with the therapist, as well as enhance treatment adherence [17]. For example, successful experiences of facing fears under hypnosis can foster trust in the hypnotherapist [23]. Moreover, positive views toward hypnosis might increase confidence in the effectiveness of therapy for certain patients [17].

Developing a sense of self-efficacy and heightened ego strengthening. Hypnotic techniques such as Ego strengthening are used to foster self-efficacy, self-esteem and self-assurance in patients. Self-efficacy provides a better quality of life, self-regulation and control and is one of the essential components in the successful treatment of anxiety disorders [23].

Self-control. Similarly, a great advantage of hypnosis is that it creates a feeling in the patients that they are in control of their difficulties, instead of being at the mercy of their symptoms [132]. Indeed, people learn to surmount their fears in trance and obtain cognitive reinforcement of their ability to cope [18].

Relaxation training. Relaxation techniques are an integral part of CBT as they help patients control their feelings of anxiety and tension [133]. For example, with the high level of arousal that PTSD patients tend to display, it can become difficult for them to fully participate in their therapy [17]. Many hypnotic techniques can serve to soothe patients and help them build personal resources [17]. For example, the patients can be taught relaxation techniques and learn the use of a safe place imaginary technique, which they can further practice by themselves using self-hypnosis [17]. Other relaxation techniques may include deep breathing, muscular relaxation and suggestions for relaxation. Hypnosis can be utilized easily in conjunction with all of these techniques.

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Imaginal exposure. Imagery is used by many CBT clinicians to facilitate anxiety reduction. The purposes of imagery are twofold: first, it can be utilized to induce relaxation by suggesting soothing and relaxing images to the patient. Secondly, imagery can be helpful for imaginal exposures, which is what is used to treat anxiety-provoking memories, images or thoughts. It consists of eliciting the patients to imagine their most feared memories or worst imagined outcome of feared situations and then to make them realize that their anxiety subsides even though they still think of the situation. By definition, hypnosis is an intense absorption into internal experiences that has the ability to create vivid images through increased body awareness, heightened suggestibility and a relaxed state [16, 21]. Also, suggestions under hypnosis can touch many aspects such as cognition, physical sensations and emotions [16]. Hypnosis can thus greatly enhance the emotional engagement of patients during exposure as well as make people experience their fears more intensely than with relaxation, which in turn could improve its efficacy [16, 21]. Hypnosis could also be used in the context of imagery rescripting therapy (IRT;23). As an imagery-based cognitive treatment, IRT employs exposure not for habituation but rather as a way for activating images, emotions, and beliefs associated with traumatic memories. Through the process of activation, the goal of this therapy is to modify and restructure the traumatic images, dysfunctional beliefs, attributions and schemas. Alladins' IRT [23] is comprised of four components: imaginal exposure, imaginal restructuring, self-calming and self-nurturing, and emotional linguistic processing. Within each of these components, well-known hypnotic techniques such as the *bubble technique* and the *comforting the child technique* can be used. For example, during the imaginal rescripting phase, the patient creates a mastery image during which the "survivor self" enters the traumatic scene to assist the "traumatized self". The integration of the *split screen technique*[6] can be used to render the traumatic event more bearable. Finally, in addition to augmenting imagination, hypnosis facilitates both non-conscious and non-linguistic information processing that are often part of traumas [23].

In vivo-exposure. In-vivo exposure is an important element of therapy for all anxiety disorders; however, this experience can be very distressing and disorienting for certain patients, and can even lead to early dropouts [80, 100]. Moreover, with patients suffering from a trauma, a degree of symptom stability, ego-strengthening and the capacity to tolerate emotionally charged imageries are required before beginning exposure therapy [17, 115]. Hypnosis can thus be used as an effective preparation tool for the expositions [17]. Indeed, hypnosis can help control and modulate the experience of patients and give them adequate tools to feel more secure and calm [100, 119]. For example, patients can learn, through self-hypnosis, to imagine a comforting and secure place in order to render their experience less distressing [17]. In addition, a patient who suffers from OCD can be instructed to touch objects which the person feels are contaminated while the hypnotherapist provides suggestions that "no harm will come to him" [132]. Through many imagined rehearsals of coping, resistant patients may become more confident in their ability to face in-vivo exposures. During exposure in PTSD, clinical psychologists must be careful not to re-traumatize the clients.

6 In the treatment of PTSD, for example, this technique involves the projection of different images of memories of the trauma on one side of an imagined screen, and on the other side something that comfort the person [23].

Hypnosis can therefore help to prevent unnecessary exposure to too many traumatic events [119]. Indeed, indirect hypnotic safeguards such as ideomotor signalling for answering specific questions (e.g. Do you feel ready to regress to the past and address some event that is necessary for healing and which you feel able to cope with at present with help?) provide the hypnotherapist with the confirmation that the patient is able to embark on age-regression of the traumatic events [119].

Cognitive restructuring. Some of the early hypnotherapists already recognized the usefulness of hypnosis for cognitive restructuring [6]. Indeed, one important part of therapy is to teach patients to monitor and recognize their maladaptive thoughts. The increased suggestibility and reduced cognitive processing that accompany hypnosis make it a tool for rapid cognitive changes [133]. Hypnotherapy can be used to teach patients to replace their negative self-suggestions (e.g." I'm not good enough to make a good presentation") with hypnotic suggestions ("I've done many of them and I've always had good feedback") that reduce their anxiety [6]. These suggestions also can be applied during self-hypnosis [6]. Hypnotic interventions also can help to strengthen patients' flexible thinking styles [134]. For example, it can help facilitate cognitive restructuring and re-appraisal of traumas; for example, through dissociation and self-distancing techniques, such as the split-screen technique, the imagination of a safe place, and the use of the "older" or "compassionate" self [17, 119]. A self-distance perspective is thought to promote insight and closure, as well as a reduction in rumination and distress [17]. With a self-distance perspective, people can come to see the situation from a different angle, which was impossible for them before as they focused on simply recounting their experience (and creating a whole lot of distressing symptoms). For example, with the use of the "compassionate self', a guilty PTSD patient can realize that he/she could not have done more and that the situation in question was out of his or her control. Another use of hypnosis is as a tool for memory integration, which can help promote cognitive restructuring [118].

Building coping skills. An important aspect of anxiety is its physical symptoms. For example, according to the DSM-IV [63], GAD is characterized by somatic symptoms such as muscle tension, irritability, insomnia and restlessness [135]. Moreover, according to cognitive-behavioural theories, PD/A is based on the acquisition of the fear of physical sensations, especially those associated with the autonomic nervous system [136]. When PDA patients feel anxious, physical symptoms such as heart palpitations, headaches, and difficulty breathing can arise [18]. Building coping skills and self-efficacy under hypnosis is an effective way to control these symptoms [18]. Recently, autogenic training was found to produce significant reductions in blood pressure and pulse rate, which are often symptoms of anxiety [137]. According to Hammond [138], autogenic training is like a "structured German form of self-hypnosis" (p.264]. Hypnosis also can be utilized to help patients manage their physical responses to anxiety provoking stimuli so that they can dissociate somatic responses to psychological distress [135].

Another coping skill that patients can acquire is to learn to redirect their attention away from distressing cues. For example, in PTSD, arousal and avoidant symptoms are triggered by both internal and external cues associated with the memories of the trauma. Unfortunately, PTSD

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patients seem to be particularly distractible to these cues and the result is that their condition cannot improve. Lynn et al. [17] propose that hypnosis can facilitate attention control in these patients so that they can stop being absorbed by cues of traumatic memories. Indeed, they propose that if it is possible to suggest to a patient to enter a state of hypnosis, it is possible to suggest that this same patient experiences enhanced attention and concentration (p.322). Thus, people under hypnosis can learn not only how to focus their attention in the moment, but also how to switch their attention away from increasingly distracting cues [17]. The latter hypnotic attentional control learning can also be useful to help patients contend with their flashbacks [17]. However, Lynn et al. [17] also propose that this technique should also be accompanied with suggestions for increased tolerance to disturbing flashbacks.

Building of social skills. Anxiety disorders can create disturbances in interpersonal relationships or even be exacerbated by a lack of social competence [133]. The teaching of social skills is thus a common component of CBT protocols. With hypnosis, the patients can practice their new social skills in imaginal rehearsals [133]. On a different level, as explained by Alladin [23], early traumas created by abuse and neglect, for example, can affect people's internal working models or relational schemas. Moreover, these core relational schemas are sometimes relatively unresponsive to verbal information or the views expressed by the patients' relatives so that when different opinions are uttered, the patient will not believe them. In conjunction with a hypnotic technique such as age regression, reframing work can be done to change some of these core beliefs.

Overcoming resistance. According to Kraft [139], hypnosis can be used as a technique to counteract resistance to therapy and exposure that is sometimes found in agoraphobics, for example. Moreover, hypnotists can resort to indirect hypnotic suggestions to counteract patients' resistance to suggestions. For example, they can paradoxically instruct a patient to continue to resist to a given suggestion in order for this individual to get some control in the decision-making during the psychological intervention. The objective is to ultimately elicit compliance [23].

Behavioural modification. Another way that hypnosis can be useful is through the administration of post-hypnotic suggestions, which works by shaping the patients' behaviours and experiences after therapy [16]. Post-hypnotic suggestions are defined as instructions to a hypnotised person to show certain behaviours or have certain experiences after hypnosis [32]. For anxious individuals, suggestions can include to experience less anxiety during their daily routines, comply with therapy homework, employ coping strategies when faced with distressing situations or stimuli, and become aware of adaptive appraisals made during times of anxiety [16]. Furthermore, the hypnotherapist can make post-hypnotic suggestions that the patient will be able to deal with adverse situations with greater confidence [17]. According to Yapko [70], post-hypnotic suggestions are widely used in hypnotherapy. So far, there is little yet increasing empirical evidence of the efficacy of post-hypnotic suggestions. For instance, recently it was discovered that post-hypnotic suggestions were capable of simulating several clinical conditions such as blindness, amnesia, auditory hallucinations, conversion disorder paralysis, selected delusions, [31, 140] and neglect-like visual behaviours in healthy patients [141]. Moreover, with highly hypnotisable participants, post-hypnotic suggestions were used to reduce the automatic tendency to read printed words in a Stroop task [142, 143], and to reduce the Simon effect, which is the facilitation of lateralized responses, when they are executed in the same side of space as that

of the stimulus [144]. The latter demonstrations thus support the clinical use of post-hypnotic suggestions to extend the achievements made during therapy.

Power of treatment. Finally, recent studies show that when used properly, hypnosis adds leverage to treatment and accelerates the recovery processes [18, 23, 27, 103]. According to Alladin [23], this is due to the fact that "hypnosis produces a syncretic cognition, which consists of a matrix of cognitive, somatic, perceptual, physiological, visceral, and kinaesthetic changes" (p.104).

5.2. Hypnotisability assessment

Different opinions remain as to whether or not levels of hypnotisability should be assessed before undergoing hypnotherapy [145]. These divergent opinions are based among other things, by the fact that some studies do report a link between levels of hypnotisability and treatment gains [102, 103] while others do not [121, 146, 147]. Moreover, researchers are facing some difficulties when trying to link hypnotisability with treatment outcomes. Indeed, one problem lies in the timing of the assessment [56]. When participants undergo a standard test of hypnotisability prior to their treatment, they are likely to infer conclusions about their own susceptibility to hypnosis. This could, in turn, influence their expectations toward the success of the treatment, which could ultimately affect their treatment outcome [56]. On the other hand, when hypnotisability levels are assessed after the treatment, the participants' experience during the treatment might then have an influence on subsequent levels of responsiveness under hypnosis [56]. On a more positive note, Lynn and Shindler [145] state that modern evaluation techniques have rendered possible the use of a good hypnotisability assessment. They also present the advantage of being able to evaluate a variety of factors (attitudes, beliefs, rapport with therapist, motivation to respond) that could influence the response to hypnosis, and to model the hypnotherapy techniques around it in order to augment the efficacy of the treatment [145]. Indeed, as it was stated before, considering participants' attitudes and expectations of hypnosis is crucial, as expectation of positive therapeutic outcome is more often than not predictive of improvement in treatment [148]. In term of hypnotisability levels displayed by participants, expectancies have also been demonstrated to play a major role [149]. Moreover, a good assessment is imperative to remove clients who are unsuitable candidates for hypnotherapy due to their conditions (e.g. patients who are more prone to psychotic decompensation, those with a paranoid level of resistance to being controlled) [145]. Needless to say, this evaluation goes beyond the simple use of formal scales of hypnotisability [145]. For guidelines on how to assess patients' level of hypnotisability, refer to Lynn and Shindler [145].

5.3. Research on hypnosis

There remains a long way to go before hypnosis as an adjunct to the treatment of anxiety disorders is considered a first-line treatment. Future research will need to conduct good quality randomized controlled trials for each of the anxiety disorders. Well-conducted multiple case studies from independent researchers also must be done to establish the validity of hypnosis as an adjunct to CBT. Studies must have adequate sample sizes so that good power can be achieved, and provide an intent-to-treat analysis in order to have better chances of finding conclusive results. They also need to have a clear detailed protocol for the hypnotic techniques used,

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for replication purposes. Moreover, as suggested by Lynn et al. [43], good descriptions of the population at hand permit replication and help in assessing the external validity of the results. Such descriptions should include the diagnostic procedures, patients' demographic and treatment history, use of medication, comorbid diagnoses, and tests administered [43]. According to Schoengerber [56], despite the difficulties met while assessing hypnotisability levels, good attempts should be made to do so. For example, the Stanford Hypnotic Susceptibility Scale-Form C (SHSSC) is considered a gold standard measure and a good individual measure, and the Waterloo adaptation of this scale, the WGSC, is good for group administration [62]. Furthermore, in order to avoid the possibility that disproportionate numbers of high hypnotisable participants end up in one group compared to another, researchers could randomly match or stratify participants in terms of their hypnotisability scores or at least report the hypnotic suggestibility of each group in terms of scores. These scores could then be used as covariates in statistical analyses if groups differ considerably on this variable [43]. As some studies seemed to indicate that the effect of adding hypnosis appeared or persisted in the long-term [15, 126], studies should include follow-up measures. In conclusion, in accordance with the Society for Clinical and Experimental Hypnosis, this chapter argues that hypnosis is a technique and not a type of therapy and that it should be used as a tool to augment the efficacy as well as the patients' understanding of CBT principles [43, 134].

6. Conclusion

Clinical hypnosis is a flourishing area of research that has so far demonstrated the usefulness of hypnosis in many domains, especially in the treatment of pain in the medical environment and during medical procedures [55]. According to Bryant [16], there is no doubt that hypnosis can ameliorate established means of treating anxiety disorders. However, more research needs to be conducted in order to provide the information necessary to establish hypnosis (added to CBT) as an empirically supported treatment for anxiety disorders. The lack of adequate studies on this topic points to the need for more rigorous randomized controlled investigations on the use of hypnosis for anxiety disorders. This chapter, as well as many other books and articles [16, 23, 94, 150] present many ways in which hypnosis can be added to CBT. Researchers who wish to study hypnosis can refer to these as guidelines.

William [6] pointed out that hypnotherapy does not need to prove that it is superior to other forms of treatment in order to have clinical value. Indeed, the goal of clinical psychology is to determine what treatments are working for which patients with which problems, and under what conditions (Lazarus, 1973; cited in 6). Moreover, as stated before, hypnosis is a very cost-effective method [43] that could represent in some cases, a rapid, non-addictive and safe substitute to the use of medication, which is particularly important given the current increase in health care costs and adverse economic conditions [138]. Another advantage of hypnotherapy is that it can be used easily outside the clinic under the form of self-hypnosis. Self-hypnosis is defined as the employment of hypnotic suggestions through self-talk or listening to a recording of hypnotic suggestions [16]. Contrary to popular belief, how intensely someone responds to hypnosis resides in the ability of the individual, rather than in

the special skills of the hypnotist [16]. Thus, self-hypnosis is a viable solution to help maintain the skills that were acquired during therapy. Consequently, hypnosis seems to respect the principle of parsimony, one of the most popular principles of clinical psychology, by creating more rapid gains and enhancing the efficacy of CBT interventions. Indeed, clinical psychologists should always try to utilize the least complex and most efficacious mode of treatment first [138].

This chapter focused on the use of hypnosis in the treatment of adult anxiety disorders. It is important to note that hypnosis is a therapeutic tool that is suitable for child and adolescent therapy. Indeed, although most research on hypnosis focus on adults, the popularity of complementary and alternative forms of therapies has started to attract parents of children with different problems [151]. According to Saadat and Kain [151], hypnosis is a suitable therapy for children because in general, they are more hypnotisable than adults. This is thought to be due to their increased capacity and willingness to become absorbed in fantasy, play, and imagination [151]. Moreover, psychologists can easily design specific hypnosis goals and suggestions that are individualized to the child and respect a developmental psychopathology perspective [152]. As for adults, meta-analyses and overviews have demonstrated the efficacy of hypnotherapy in treating children medical conditions such as asthma, chronic and acute pain, along with procedure-related distress for cancer patients [3]. Hypnosis also has improved child behavioural conditions such as trichotillomania, thumb-sucking, enuresis, dysphasia and chronic dyspnea [151]. However, Huynh et al's. [3] review of the literature revealed no randomised or controlled trials on the use of hypnotherapy for children with psychiatric disorders. Still, a high number of case reports indicated that hypnotherapy can be useful in treating children with PDA, social and specific phobias, OCD, GAD, and PTSD [3]. However, as is the case for adult anxiety disorders, the addition of hypnosis to clinical practice for children and adolescents needs to be developed and studied further before it is recognized as an empirically supported treatment.

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Chapter 15

Current State of the Art in Treatment of Posttraumatic Stress Disorder

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Additional information is available at the end of the chapter

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1. Introduction

Posttraumatic stress disorder (PTSD) is the most common mental health problem among people exposed to traumatic events. Since its introduction into the psychiatric classification system in the 1980s various treatments have been tested for PTSD. Meta-analyses based on randomized controlled trials (RCTs) concluded that trauma-focused psychotherapies are most effective treatments for PTSD [1-3]. The most widely used trauma-focused psychotherapies are exposure treatment, cognitive therapy, cognitive behavioural treatment (CBT) involving a combination of exposure and cognitive interventions, and Eye Movement Desensitization and Reprocessing (EMDR). In this chapter we briefly review these treatments in terms of their theoretical background, application, efficacy, tolerability, and length of delivery.

2. Trauma-focused psychotherapies

2.1. Exposure treatment

Exposure based interventions have the largest evidence base and received the strongest empirical support for efficacy in treatment of PTSD as well as other anxiety disorders [4, 5]. Exposure treatment has its theoretical foundation in learning theory of fear acquisition and extinction. Basically, learning theory holds that fear is learned through classical conditioning and systematic exposure to feared stimulus without any adverse consequence results in progressive reduction in the fear response (i.e. extinction or habituation of fear response). The mechanism of exposure treatment is now explained with the concept of habituation and corrective learning in the widely known *emotional processing theory* developed by Foa and colleagues [6, 7]. According to this theory, fear is represented in memory as a structure consisting of informa-

tion about (a) the feared stimulus, (b) verbal, physiological, and motor responses, and (c) their interpreted meaning [8, 9]. Exposure therapy exerts its effect through activation of the 'fear structure' and integration of corrective information that is incompatible with it (e.g. disconfirmation of overestimated probability of harm) [6]. Successful exposure therapy does not abolish pathological associations in the fear structure, but rather establishes new, non-pathological ones [7]. In other words, fear reduction implies new learning, not unlearning. Three indicators of emotional processing determine successful learning and thus outcome of exposure therapy: (a) initial fear activation (i.e. physiological arousal in response to feared stimulus), (b) within-session habituation of anxiety (i.e. fear reduction during exposure to feared stimulus), and (c) between-session habituation (i.e. reduction in initial fear response across sessions) [6]. Within-session habituation helps dissociating the stimulus from fear response and between-session habituation forms the basis for long-term learning by providing opportunities of change in the meaning of the association between stimulus and fear response (i.e. lowered expectation of harm and lessened valence, negativity, of the stimulus). Within-session habituation is a necessary prerequisite for between-session habituation.

Although the contemporary learning theory provides the most validated, comprehensive, and plausible theory of anxiety disorders [10, 11], the emotional-processing theory has received partial support. In an extensive review of clinical studies that examined the contribution of three indicators of learning to treatment outcome, Craske and colleagues found only weak support for the premises of emotional processing theory [12]. The authors found no consistent evidence to support or refute the role of initial fear activation. While within session-habituation often occurs, the amount by which fear declines or the level of fear on which a given exposure trial ends does not predict overall improvement. Hence, within session-habituation appears to be mediated by mechanisms that are different than the mechanisms responsible for long-term outcomes. Although some studies show that the amount by which fear is reduced across occasions of exposure (between-session habituation) predicts treatment outcome, other studies indicate that improvement occurs despite lack of significant reductions in parameters of fear (e.g. heart rate or skin conductance) between exposure sessions. Finally, the authors found no evidence for the premise that within session-habituation is a necessary precursor to between-session habituation. On the basis of these findings and the literature documenting the context-specific nature of fear extinction [13], it has been suggested that that there is a need to shift away from an emphasis on fear reduction during exposure therapy to a new exposure paradigm which emphasizes attenuating avoidance behaviour and strengthening anxiety and fear tolerance [12, 14]. This is consistent with experimental work with animals which show that unpredictable and uncontrollable stressors play an important role in the development of anxiety and fear responses [15, 16] and the evidence from research with trauma survivors suggesting that lack of sense of control over traumatic stressors is the critical mediating factor in PTSD [11, 17-20]. Thus, helping the person regain control over traumatic stressors might therefore reduce traumatic stress [15, 21].

The goal of classic exposure therapy in PTSD as practised today is to promote anxiety reduction through habituation and emotional processing of trauma memory [22]. This is achieved by imaginal exposure to trauma memory and live exposure to trauma reminders. In imaginal exposure the survivor recounts anxiety evoking memories about the traumatic event in a

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systematic, prolonged and repetitive manner, while in live exposure s/he confronts anxiety evoking reminders of the traumatic event. Most treatment protocols combine imaginal and live exposure, while a few incorporate only imaginal exposure [23-25]. The way imaginal and live exposure is implemented shows great variability across programmes. For instance, in the widely used *Prolonged Exposure* programme developed by Foa and colleagues [26], live exposure is introduced simultaneously with imaginal exposure and imaginal exposure is followed by a discussion of emotional responses to trauma memory. In the *Exposure Therapy* protocol of Marks and colleagues [27], on the other hand, live exposure is introduced midway in the treatment following 5 sessions of imaginal exposure and emotional responses to trauma memory are not discussed at any stage. Many treatment programmes that are largely based on these two protocols also employed additional interventions such as anxiety management techniques (e.g. relaxation training, coping skills training, breathing training, thought stopping, and guided self-dialogue) [28, 29], cognitive restructuring [30-33], supportive counselling [23] and imagery rescripting (i.e. developing a positive alternative visual representation of oneself coping more effectively with the trauma during and / or after its occurrence) [34, 35]. Relatively little research has been conducted to examine the contribution of these techniques to improvement. While some evidence suggests that adding cognitive restructuring to exposure enhances treatment effects [23], other studies show that cognitive interventions [27, 36, 37] or various anxiety management techniques [38] do not confer additional benefits when used in combination with exposure.

Considering the problems associated with the habituation model and the findings on the importance of sense of control in trauma survivors (reviewed above), Basoglu and colleagues [21, 39-41] modified exposure treatment by: (a) focusing on only behavioural avoidance in treatment (i.e. live exposure to trauma cues), thereby eliminating treatment ingredients that rely on heavy therapist input and pose challenges of practicability in different post-disaster and cross-cultural settings; and (b) shifting treatment focus from habituation to feared stimuli to enhancement of 'sense of control' over them. The underlying principle of the new *Control-Focused Behavioural Treatment* is to enhance a person's resilience against traumatic stressors by helping them to develop sense of control over them. This can be achieved by exposure to either (a) unconditioned stimuli in a safe and controlled environment (i.e. the original traumatic stressor in simulated form or in virtual reality settings) or (b) conditioned stimuli (e.g. trauma reminders) that possess the distress-evoking characteristic of the unconditioned stimuli until the person is able tolerate and control associated distress [42]. To this end treatment targets behavioural avoidance of trauma reminders and mainly involves therapist-delivered instructions for self-exposure to feared and avoided situations until the survivor is able to tolerate and feel in control of anxiety or fear (rather than until 'fear is reduced'). The findings from clinical trials (reviewed below) showed that *Control Focused Behavioural Treatment* has promise in treatment of mass trauma survivors.

2.2. Cognitive therapy

Cognitive therapy of anxiety disorders is based on the understanding that anxiety occurs due to selective processing of information in the environment perceived as signalling threat or

danger to the individual and such cognitive biases can be corrected through conscious reasoning [43, 44]. The cognitive model of PTSD views anxiety as an outcome of maladaptive appraisals about trauma and its consequences and attributions centring on danger and threat [45]. In addition, traumatic events are believed to shatter people's basic beliefs and assumptions about themselves, the world, and others [46]. Therapy is thus designed to restructure or correct dysfunctional ways of thinking that cause distress, anxiety, or fear. The survivor is taught to challenge dysfunctional thoughts or beliefs through Socratic reasoning, test their accuracy through behavioural experiments in situations perceived threatening or dangerous, and replace them with alternative ones that better reflect reality.

Empirical support for cognitive theory of PTSD is rather weak. No prospective study with pre- to post-trauma assessments tested whether traumatic events shatter basic beliefs and assumptions. Although survivors with PTSD tend to report more negative beliefs [47-49] or information processing biases [50-52], there is not sufficient evidence to refute the argument that these may be epiphenomena of traumatic stress problems, rather than being a cause of them. Research on this issue that employed statistical controls to examine the role of all possible contributing factors to the disorder (e.g. demographic, personal history, trauma exposure characteristics etc.) did not indeed find a strong association between beliefs and PTSD [18, 20]. Furthermore, exposure, though referred to as *behavioural experiment*, is considered a necessary component of cognitive therapy for successful treatment because it allows better processing of threat [43, 44]. As exposure's efficacy is already established in anxiety disorders, it is difficult to attribute successful treatment outcome in cognitive therapy to cognitive change. Furthermore, even when treatment protocols do not directly involve an exposure component, they may indirectly trigger it. Similarly, exposure therapy alone may provide an opportunity to test dysfunctional appraisals about trauma and thereby lead to cognitive change. Comparative studies found cognitive therapy as effective as exposure [27, 53, 54]. However, the fact that no study examined whether cognitive therapy instigated self-exposure in between sessions among treated cases preclude a definitive conclusions about the importance of cognitive change in treatment. On the other hand, there is evidence showing that exposure treatment without cognitive restructuring produce as much cognitive change as exposure with cognitive restructuring [37, 55, 56]. Reductions in negative cognitions were significantly related to reductions in PTSD symptoms in these studies, suggesting that cognitive change occurs as a response to improvement in PTSD and not vice versa. These findings support the view that cognitive responses to trauma are epiphenomena of traumatic stress.

As exposure protocols, cognitive therapy programmes for PTSD differ in their specifics. The *Cognitive Therapy* programme developed by Ehlers and colleagues [57, 58] and *Cognitive Processing Therapy* developed by Resick and colleagues [53] involve imaginal exposure to the traumatic memory, but this is limited to only a few sessions and the focus of imaginal reliving is to teach the survivor modify their beliefs about the meaning of the traumatic event. The Ehlers et al programme also involves some unsystematic live exposure (e.g. visiting the site where the trauma happened). Other cognitive therapy protocols do not involve any exposure elements [24, 27].

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2.3. Eye Movement Desensitization and Reprocessing (EMDR)

The field of PTSD treatment witnessed a rapid growth of new treatment protocols, the most studied of which is undoubtedly EMDR. EMDR is an information processing therapy during which the patient recounts trauma story with its cognitive, affective, and physiological features while simultaneously focusing visually on bilateral movements of an external stimulus until the distress evoked by traumatic memory subsides [59]. The EMDR theorists maintain that the eye movements reduce the distress associated with trauma memories and help cognitive and emotional reprocessing of the traumatic event. EMDR combines multiple theoretical perspectives and techniques, most pronouncedly imaginal exposure and cognitive restructuring. Proponents of EMDR hold that the very brief and interrupted nature of imaginal exposure in EMDR sessions is at stark contrast with the behaviour therapists' requirement of prolonged and uninterrupted exposure to achieve habituation and disconfirmation of fear-expectancies [5, 6]. However, research on the processes of change in exposure treatment has not been conclusive regarding these requirements [12, 60]. EMDR proponents also contend that the use of directed eye movements distinguishes this form of therapy from other cognitive behavioural approaches. However, the role of eye movements in treatment has not been theoretically clarified and the findings of dismantling studies (reviewed in a meta-analysis) suggest that the eye movements are neither necessary nor sufficient to treatment outcome [61].

2.4. Other trauma focused interventions

Some treatment programmes for PTSD combined different components of existing treatment protocols under a different name (e.g. *Cognitive-Behaviour Trauma Treatment Protocol* [62], *Trauma Focused Group Psychotherapy* [32], *Direct Therapeutic Exposure* [33]. Some other new protocols, on the other hand, mainly embodied some form of exposure and cognitive restructuring, but these were presented with a different rationale for efficacy and they varied in the procedures of implementation (e.g. *Narrative Exposure Therapy* [63], *Imagery Rehearsal Therapy* [64], *Image Habituation Training* [65, 66], etc.). Although they look like new treatment approaches, these are mainly modified forms of existing treatments for PTSD. Also, few are grounded in theories of aetiology of PTSD and related empirical support.

2.5. Evidence base of trauma-focused psychotherapies

As noted earlier, several meta-analyses of randomised controlled trials showed comparable efficacies for various trauma-focused psychotherapies [1-3]. These meta-analyses, however, did not examine the efficacy of various treatment packages with respect to their main components. Such examination is important in clarifying the ingredients that are most useful for achieving maximum efficacy. Such knowledge also has important implications for refining theories of PTSD. To identify the contribution of each component to treatment efficacy we conducted a comprehensive literature review of randomized controlled trauma-focused treatment studies of PTSD. These studies were selected through a literature search of randomized controlled trials of CBT in PsycInfo (1806 – 2009), PILOTS (1960 – 2009), and PubMed (1966 – 2009) databases. To be included in the meta-analysis the study must have (a) tested the efficacy of a treatment for PTSD against a control group, waitlist or placebo

treatment or alternative intervention, or combination of any of these, using a randomized controlled trial design, (b) included adults who met diagnostic criteria for acute (1 to 3 months post-trauma) or chronic (more than 6 months post trauma) PTSD as defined by DSM-III, DSM-IIIR, DSM-IV, or DSM-IVTR, (c) used valid structured interview forms and / or self-rated instruments for the assessment of PTSD, (d) its sample size was large enough to allow sufficient power in analyses (i.e. at least 8 patients in each group), (e) provided sufficient data in the article for calculation of effect sizes or through contact with authors, and (f) has been published in English. This search revealed 41 studies that met the inclusion criteria. We analysed them meta-analytically by combining their findings using the standardised effect size statistic. Effect size is a measure of the strength or magnitude of a treatment effect and one way to calculate it is by computing the difference between pre- and post-treatment means on outcome measures and dividing this by the pooled standard deviation of those means [67]. This method can also be used to calculate the effect size between two treatment conditions. Effect size values of 0.20 indicate small, 0.50 moderate, and 0.80 large treatment effects. Larger effect sizes indicate more symptom reduction and less residual symptoms at the end of treatment. As various clinician-rated and / or self-rated instruments were used to assess PTSD we computed an aggregate effect size over all PTSD measures employed in a study. Data were analysed using SPSS 14.

Table 1 shows the number of participants, attrition rates, treatment duration (number of sessions and total hours spent), and effect sizes for PTSD and depression from baseline to post-treatment for main treatment components of 41 randomized controlled trials. Studies involving *Control-Focused Behavioural Treatment* [21] are excluded from this meta-analysis due to its theoretical difference from other treatment protocols and brevity (i.e. single-session application). These studies are reviewed separately in Section 2.6. Treatments in Table 1 were tested with survivors from a wide range of trauma events, including war veterans, rape victims and survivors of childhood abuse, survivors of civilian trauma (e.g. physical assault, crime, traffic accident, etc.), and refugees. Exposure-based interventions were tested with all these trauma survivors, whereas cognitive treatments and EMDR were mainly tested with survivors of rape and civilian trauma. Control conditions involved waiting list and non-specific treatments such as relaxation, supportive counselling, and present-centred therapy (i.e. coping and problem solving skills training).

	N conditions	Sample Size	Attrition rate	N sessions	Treatment duration		Effect size[a] Mean (SD)
Main treatment components			**%**	**Mean (range)**	**Hours Mean (SD)**	**Weeks Mean (Range)**	**PTSD**
Imaginal exposure[1]	6	105	20	8.5 (4-14)	11.8 (6.6)	9 (3-23)	0.86 (0.39)
Imaginal + live exposure[2]	11	317	25	10 (5-20)	16.5 (9.2)	9 (4.5-16)	1.98 (0.69)

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	N conditions	Sample Size	Attrition rate	N sessions	Treatment duration		Effect size[a] Mean (SD)
Main treatment components			**%**	**Mean (range)**	**Hours Mean (SD)**	**Weeks Mean (Range)**	**PTSD**
Imaginal exposure + cognitive restructuring[3]	4	165	20	17 (8-30)	29.6 (21.7)	17 (9-30)	1.29 (1.11)
Live exposure + cognitive restructuring[4]	2	64	16	11 (--)	16.5 (0.0)	5.5 (--)	3.80 (0.83)
Imaginal + live exposure + cognitive restructuring[5]	10	193	32	11 (4-20)	18.5 (9.9)	12 (4-18)	1.74 (0.48)
Cognitive therapy without exposure[6]	2	51	8	11 (10-12)	13.5 (2.1)	21 (16-26)	1.41 (0.35)
Cognitive therapy with limited imaginal / live exposure[7]	4	107	19	16 (12-27)	18.1 (11.6)	12 (6-17)	2.42 (0.67)
Imaginal & live exposure + anxiety management[8]	2	34	17	8 (7-9)	12.0 (2.1)	6 (5-7)	1.78 (0.30)
Imaginal exposure + skills training[9]	2	33	32	25 (16-34)	37.5 (19.1)	15 (12-17)	1.16 (0.87)
Imaginal exposure + imaginal rescripting[10]	2	76	31	6.5 (3-10)	11.0 (5.7)	7.5 (5-10)	1.09 (0.31)
EMDR[11]	12	199	16	6 (2-12)	8.5 (4.6)	6 (2-10)	1.66 (0.94)
Control Conditions							

	N conditions	Sample Size	Attrition rate	N sessions	Treatment duration		Effect size[a] Mean (SD)
Main treatment components			**%**	**Mean (range)**	**Hours Mean (SD)**	**Weeks Mean (Range)**	**PTSD**
Relaxation[12]	4	59	11	10 (8-12)	11.7 (3.5)	10 (6-16)	0.75 (0.61)
Supportive counseling[13]	4	66	18	8 (5-10)	11.4 (3.0)	6 (4-10)	0.60 (0.32)
Present centered therapy[14]	3	268	18	18 (9-30)	27.8 (15.8)	20 (10-30)	0.70 (0.48)
Treatment as usual[15]	2	47	7	--	--	--	0.69 (0.58)
Waitlist / minimal attention control[16]	25	516	11	--	--	--	0.27 (0.38)

[a] Calculated from the raw data reported in the articles. Where data were provided only in graphic form, raw data were obtained from the authors. For articles reporting effect sizes without reporting any data, effect sizes as reported in the published article were used.

1= [23, 25, 34, 54, 63, 65], 2 = [26, 27, 36-38, 53, 89, 107-110], 3 = [23, 32, 33, 111], 4 = [112, 113], 5 = [27, 30, 31, 36, 37, 62, 114-117], 6 = [27, 54], 7 = [53, 57, 118, 119], 8 = [29, 38], 9 = [28, 33], 10 = [34, 64], 11 = [29, 62, 65, 108, 110, 116, 120-125], 12 = [27, 65, 110, 120], 13 = [23, 26, 63, 114], 14 = [32, 115, 126], 15 = [31, 123], 16 = [25, 26, 28, 30, 33, 36, 38, 53, 57, 63, 64, 89, 108, 111-116, 118-122, 124]

Table 1. Evidence base for trauma-focused interventions

All active treatments yielded larger effects on PTSD than did control conditions. Although all treatments achieved clinically large effect sizes (over 0.80) in PTSD, they differed in their efficacy. Imaginal exposure and cognitive therapy had limited efficacy compared with other treatments when they were used alone. Although the addition of cognitive restructuring, skills training, and imagery rescripting enhanced the efficacy of imaginal exposure, treatment effects still remained limited. On the other hand, the efficacy of both imaginal exposure and cognitive therapy reached their maximum when they were combined with live exposure (1.98 and 3.80, respectively). These findings imply that live exposure is the critical ingredient in CBT packages. Cognitive therapy programmes involving an exposure component also performed significantly better than cognitive therapy alone, suggesting that cognitive interventions by themselves are not sufficient for successful treatment outcome. The addition of other interventions to full exposure programmes did not lead to better outcomes (they even compromised treatment gains). EMDR was also effective in PTSD, however it was associated with more residual symptoms than the potent forms of exposure based treatments with or without

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cognitive restructuring. It is also noteworthy that the evidence base for exposure treatments involves more methodologically rigorous studies than that of EMDR.

It is worth noting that the effect sizes reported in Table 1 are based on cases that completed a given programme during a RCT. As 8% to 32% of the patients dropped out of the studies, the composition of the experimental groups can no longer be considered random, which creates a selection bias reflecting the outcome of those who remain in the study or who respond to the specific treatment [68]. Findings based on more conservative intent-to-treat (or last observation carried forward) analyses, which include non-treated or non-treatment-responder cases, are more attenuated. For example, the effect sizes for imaginal and live exposure and cognitive therapy with limited exposure programmes in studies that reported intent-to-treat analyses were 1.23 (n = 4) and 1.80 (n = 3), respectively. We selected to report findings based on completers analyses because we were interested in seeing treatment outcome among those who received the full treatment. Also, intent-to-treat analyses were not consistently reported in all articles.

Tolerability of a treatment as indicated by attrition rates is an important parameter in evaluating treatment protocols. Attrition rates varied across treatment protocols but the differences were not statistically significant. When we grouped interventions, the average rate of dropout was 25% from treatment packages involving an exposure component (including cognitive therapy with limited exposure), 8% from cognitive therapy and, 16% from EMDR. Although it seemed that interventions involving exposure were less tolerable, this finding needs to be cautiously interpreted because they were examined in a total of 43 trial conditions compared with only 2 cognitive therapy and 12 EMDR conditions. In addition, the number of participants in exposure was 5.5 to 21 times higher than those in EMDR and cognitive therapy (1094 vs 199 and 51, respectively).

Treatments showed great variability with respect to number of sessions and time to recovery they required. Interventions involving exposure and cognitive therapy were delivered in a mean 12 sessions, while EMDR was administered in an average of 6 sessions. Treatment lasted an average of 16 hours (SD = 11) in exposure, 20 (SD = 12) hours in exposure with cognitive interventions, 13.5 (SD = 2.1) in cognitive therapy, and 8.5 (SD = 4.6) in EMDR. Treatment delivery in these interventions took a mean of 9 (SD = 5), 12 (SD = 6), 21 (SD = 7), and 6 (SD = 3) weeks, respectively. Although delivered in about the same number of sessions, cognitive interventions required more time in treatment than did exposure alone. Cognitive therapy alone achieved relatively limited effects in a longer period of time than did all other treatments. EMDR appeared to be the briefest treatment.

Treatment programmes reported in Table 1 vary in their complexity for training. Although practice varies, more complex treatment programmes require more time for training and supervision and they are therefore more difficult to disseminate. There is not much information on the duration of various training programmes. The most common exposure protocol used with trauma survivors, prolonged exposure [26] and cognitive therapy [58] require 5 days of training each [36]. Combined treatments take longer time for training. EMDR Institute's website states that EMDR basic training is completed in 40 hours and 2-day workshops are held for advanced training. The complex procedures involved in conduct-

ing imaginal exposure and cognitive restructuring pose challenges in training of lay therapists. All these treatments also require continuous supervision. Furthermore, they rely on heavy therapist input and as such they are not suitable for dissemination on a self-help basis.

The cross-cultural applicability of these interventions is largely unknown as they were mostly tested in western countries. As exposure therapy targets universals of human behaviour (fear and avoidance) it would be expected to have promise in different cultural settings. On the other hand, it is difficult to make predictions about cognitive interventions, because cross-cultural validity of the so called maladaptive / faulty thinking patterns about trauma and its sequelae is not known. Furthermore, requirements of keeping homework sheets [26, 53] and heavy writing tasks involved in some treatment protocols [53] may complicate their practicability among survivors with low level of education that characterize populations of developing countries. They also pose challenges of use under difficult post-disaster or post-war settings, where survivors deal with day-to-day survival problems. Finally, the efficacy of these treatments has rarely been examined in survivors of natural disasters and war.

2.6. Control-focused behavioural treatment

Control-Focused Behavioural Treatment was tested in two open and two randomized clinical trials involving 331 earthquake survivors with chronic PTSD. In an open trial [39], among survivors with a PTSD diagnosis, the probability of clinically significant improvement was 76% after one session and 88% after two sessions, reaching 100% after four sessions. This improvement corresponded to a mean 57% reduction in PTSD symptoms, 69% in fear and avoidance behaviours, and 50% in depression. The mean number of sessions required for improvement was 1.7. In a subsequent randomized controlled trial *Control-Focused Behavioural Treatment* achieved improvement in 80% of survivors when delivered in a *single session* [40]. In the latter study, behavioural avoidance was the first symptom to improve early in treatment (6 weeks), followed by improvement in re-experiencing and hyperarousal symptoms [69]. Thus, reduction in avoidance appeared to be the critical factor that initiated the process of improvement in other symptoms. Further studies showed that treatment effect could be enhanced by 20% by an additional session involving therapist aided exposure to simulated earthquake tremors in an earthquake simulator [41, 70]. Improvement was maintained in the long-term in all studies, despite further exposure to numerous aftershocks and expectations of another major earthquake. An average of 6 sessions of *Control-Focused Behavioural Treatment* achieved similar improvement rates in asylum-seekers and refugees in Turkey, despite adverse psychosocial and economic circumstances [21, 71]. These findings suggested that *Control-Focused Behavioural Treatment* has promise in treatment of mass trauma survivors in non-western settings. The single-session application of *Control-Focused Behavioural Treatment*, which emphasizes self-conducted exposure in survivors' daily routine, has promise of easy distribution to large number of survivors in mass disaster settings. Further studies are needed to confirm these findings in different trauma populations living in different cross-cultural settings.

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3. Pharmacotherapy of PTSD

According to pathophysiological theories, PTSD symptoms occur as an outcome of excessive activation of the amygdala by stimuli that are perceived to be threatening. The key psychobiological systems that are believed to be altered in PTSD are adrenergic, hypothalamic-pituitary-adrenocortical (HPA), glutametergic, serotenergic, and dopaminergic systems. Various pharmacological agents therefore aim to intervene disruptions in these systems. Before 2000 a handful of randomized controlled trials reported some beneficial effects of tricyclic antidepressants. With the introduction of *Selective Serotonin Reuptake Inhibitors* (SSRI) in the treatment of anxiety disorders, researchers lost interest in studying these medications because SSRIs had more tolerable side effects and pharmaceutical companies are more eager to provide funding for research on these medications [72]. SSRIs are now indicated as the pharmacotherapy of choice in several clinical practice guidelines for PTSD [72-74]. Recently, the efficacy of newer antidepressants, including serotonin-norepinephrine reuptake inhibitors (SNRIs, venlafaxine) and noradregenic and specific serotonergic agents (NaSSA, mirtazaine) has also been examined. In addition, some atypic antipsychotic medications (risperidone and olanzapine) have been tested as adjunctive agents for refractory patients who have failed to respond to antidepressants. In this section we review the evidence from double-blind placebo controlled randomized clinical trials of SSRIs, SNRIs, NaSSa, and atypical antipsychotics. These agents are selected for the review because other drugs (e.g. anticonvulsant / antikindling agents, monoamine oxidase inhibitors, etc.) have been mostly tested in case studies or open label trials. Benzodiazepines are not included in the review because they were not found to be effective in PTSD [72]. The same methodology described above for trauma-focused therapy protocols was followed.

Table 2 lists 21 studies that tested the efficacy of antidepressants and antipsychotics combined with antidepressants in double-blind placebo controlled randomized controlled design. Treatment duration varied between 4 to 16 weeks. The attrition rates for drug and placebo were 31% (SD = 7%, range 13-47%) and 29% (SD = 14%, range 0-59%), respectively. These figures were slightly higher than those reported in psychotherapy trials. Mean reduction in PTSD symptoms was 38% (SD = 16.5) in cases treated with active drugs, while it was 28% (SD = 14.1) in cases given pill placebo. Thus, drug-placebo difference was only 10%. This pattern of improvement was also noted in effect sizes (these were calculated using change scores as described by Kazis et al. [75], because drug trials did not always report post-treatment scores). Although the majority of the drugs achieved large pre- to post-treatment effects, so did the pill placebo. Indeed, the between-treatment effect sizes rarely exceeded the threshold (i.e. 0.50) necessary to detect a clinically significant difference between an active drug and placebo. This is in contrast with exposure-based treatments which yielded much larger effect sizes. It is worth noting, however, drug trials based their findings on all cases that completed at least one assessment after baseline, thus including the cases that dropped-out from treatment by carrying their last observation forward in the data set. Even though this conservative analysis strategy may counteracted drug efficacy compared to trauma-focused psychological treatments, evidence shows that treatment effects are more stable in the latter. There are no studies that examined relapse rates in drug-free follow-ups. Few double-blind placebo controlled

		Drug			Placebo			Drug vs Placebo
	N studies	n	% Change[b]	Effect Size Mean (SD)	n	% Change[b]	Effect Size Mean (SD)	Effect Size Mean (SD)
Sertraline[1]	5	*471*	36	1.54 (0.69)	*474*	29	1.30 (0.63)	0.31 (0.20)
Fluoxetine[2]	5	*464*	44	2.35 (0.38)[c]	*245*	32	1.83 (0.39)[c]	0.62 (0.37)[d]
Paroxetine[3]	3	*541*	44	1.77 (0.69)	*363*	30	1.22 (0.41)	0.57 (0.31)
Venlafaxine[4]	2	*340*	57	3.16 (0.54)	*347*	48	2.61 (0.40)	0.48 (0.04)
Mirtazapine[5]	1	*17*	35	1.06 (--)	*9*	17	0.86 (--)	0.60 (--)
Risperidone augmentation[6]	4	*67*	26	0.99 (0.60)	*63*	21	0.87 (0.44)	0.26 (0.53)
Olanzapine augmentation[7]	1	*10*	17	0.67 (--)	*9*	3	0.16 (--)	0.75 (--)

[a] Effect sizes calculated from the raw data reported in the articles. Within group effect sizes calculated as mean change score divided by the standard deviation of the baseline score. Between-groups effect sizes were calculated as mean change score between drug and pill placebo groups divided by standard deviation of the baseline score for placebo group.

[b] Percent reductions in PTSD symptoms pre- to post-treatment

[c] Within treatment effect sizes for one study (van der Kolk et al, 1994) were not available and thus excluded.

[d] Drug vs placebo effect size for one study (van der Kolk et al, 1994) taken from [127]

1 = [128-132], 2 = [125, 133-136], 3 = [137-139], 4 = [132, 140], 5 = [141], 6 = [142-145], 7 = [146]

Table 2. Effect sizes in double-blind randomized controlled trials of pharmacotherapy for PTSD[a]

maintenance studies involving survivors treated with SSRIs found that discontinuation of drug treatment is associated with return of PTSD symptoms [76-78].

The augmentation of antidepressant treatments with atypical antipsychotics in treatment refractory patients did not also result in better outcomes, except for one study which involved only a small number of survivors. Antidepressant treatment (paroxetine) did not also augment treatment effects in patients who remained symptomatic after 12 weeks of exposure treatment [79](not listed in Table 2). On the other hand, adding exposure treatment to SSRI treatment conferred additional benefits in patients who did not respond to previous pharmacotherapy [80, 81].

A problem concerning pharmacotherapy clinical trials in PTSD is that the findings have limited generalizability because most studies involved middle-aged females sexually abused as children or Vietnam Veterans [72]. There is also less evidence on the efficacy of medications in different age groups, because concerns about increased suicides among children and adolescents treated with SSRIs for depression and concerns about safety, age-related pharmacokinetic capacity, drug-drug interactions, and comorbid medical conditions in elderly people,

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pose obstacles to pharmacotherapy research in these populations [72]. Finally, when used in combination with exposure-based treatments, drugs may undermine the efficacy of the latter by facilitating attributions of improvement to the tablets rather than to personal efforts. In view of these findings, use of antidepressants as a first-line intervention in treatment of trauma survivors could hardly be justified.

4. Other psychological treatments

There are various other interventions used with trauma survivors, which vary greatly in their emphasis in treatment. Some of these treatments aim to increase general well-being of survivors (e.g. psychosocial support, psychoeducation, normalisation, art therapy or other expressive recreational activities, etc.) or alleviate general psychological distress (e.g. coping skills training, affect management, counselling, family therapy, etc.), while others target specific psychopathology such as PTSD and depression (e.g., interpersonal psychotherapy, school based intervention for children, brief eclectic psychotherapy, etc.). Most of these treatments involve a mixture of diverse interventions without a well-defined theoretical framework. This is an important problem because a treatment could only achieve partial effects unless its mechanisms of action match the causal processes that underlie a mental health problem [82]. Furthermore, as they do not specifically target trauma induced anxiety and fear reactions, many treatments achieve low improvement rates. One example of such treatments is school-based intervention programme developed for children. This treatment mainly involves psychoeducation, normalisation of trauma reactions through creative-expressive activities (e.g. play, art therapy), and skills training. Two RCTs that tested the efficacy of this intervention in child survivors of war in Bosnia [83] and political violence in Indonesia [84] found only small to moderate treatment effects in PTSD symptoms compared to waitlist controls (effect sizes = 0.22 and 0.51, respectively). Similar moderate treatment effects were obtained in other RCTs of a psychosocial intervention program for female survivors of war in Bosnia [85] and an affect management treatment in child sexual abuse survivors [86].

A misplaced focus in treatment also occurs when specific psychiatric disorders other than PTSD are targeted. The findings of two RCTs are cases in point. In one of the studies [87], depressive symptoms were targeted with group interpersonal psychotherapy and creative play in Ugandan adolescent war survivors. Creative play showed no effect on depression severity, while interpersonal group psychotherapy reduced depression in girls but not in boys. Neither treatment resulted in significant improvement in anxiety, conduct problems, and psychosocial functioning. Targeting depression with a self-management treatment also failed to reduce depression, PTSD, and psychosocial functioning in adult male veterans [88]. These limited treatment effects could be explained by a misplaced focus in treatment.

There is some evidence suggesting that trauma focused psychodynamic therapy and brief eclectic psychotherapy combining psychodynamic therapy with cognitive restructuring and imaginal exposure are effective in PTSD. In three RCTs, compared to waitlist controls, these treatments achieved medium to large treatment effects in PTSD symptoms (range 0.66-0.94)

[89-91]. Methodological problems preclude definitive conclusions about the effects of these treatments. It is also worth noting that treatment was delivered in 16 to 20 sessions. Considering that exposure based treatments achieve higher treatment effects when delivered in a mean of 12 sessions, the usefulness of psychodynamic or eclectic approaches become questionable.

A widely used treatment approach for refugees and survivors of torture in rehabilitation centres around the world is multi-disciplinary treatment, including social, legal, medical, and psychological aid for survivors. An open outcome evaluation study based on 55 persons admitted to the Research Centre for Torture Victims in Denmark in 2001 and 2002 showed no improvement in PTSD, depression, anxiety or health-related quality of life after 9 months of treatment, leading the authors to conclude that future studies are needed to explore effective interventions for traumatised refugees [92]. In a more recent non-random quasi experimental study of torture survivors in Nepal, multi-disciplinary treatment reduced non-specific somatic problems related to torture, but not more severe specific mental health problems, including PTSD and depression, and associated disability [93]. The authors concluded that evidence-based treatments that are able to address specific mental health problems and associated disability need to be investigated for torture survivors.

5. Interventions to prevent the development of PTSD

5.1. Critical incident stress debriefing

Critical Incident Stress Debriefing has been a widely used psychological intervention after mass trauma events. In this approach survivors exposed to similar traumatic experiences participate in a structured session where they talk about the traumatic event in detail. This session, which takes place soon after the trauma, is said to allow venting of survivors' emotions about the traumatic incident within the context of psychosocial support from others and attenuate the intensity of acute stress reactions, thereby reducing the risk of developing PTSD [94]. Two RCTs with individual trauma survivors [95, 96] and one RCT with deployed soldiers [97] did not find beneficial effects of debriefing in preventing or improving PTSD symptoms. These findings led major clinical guidelines for Acute Stress Disorder (ASD) and PTSD not to recommend the use of debriefing following traumatic events [73, 98].

5.2. Brief CBT

Condensed forms of treatment based on cognitive-behavioural principles have been tested in survivors with ASD (i.e. within 1-month post-trauma) or acute PTSD (i.e. within 3 months post-trauma). Treatment packages, usually delivered in 4 to 5 sessions, involved psychoeducation; breathing, relaxation, anxiety management training; cognitive restructuring; imaginal and live exposure. A meta-analysis of the efficacy of these interventions in ASD with respect to control groups is reported in Table 3. The latter included repeated assessment (1 study), supportive counselling (5 studies), and waiting list (1 study). As the outcome was similar across all controls they were pooled for the meta-analysis. Brief CBT and prolonged exposure

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(imaginal + live exposure) achieved large treatment effects in PTSD severity and moderate effects in depression both at post-treatment and 6-months post-trauma. More survivors in the control groups met diagnostic criteria for PTSD at post-treatment and follow up. It is worth noting that the effect sizes in Table 3 are based on those who completed treatment and more conservative intent-to-treat analyses do not always yield favourable outcome for treatment [99]. Also, between-groups differences disappeared at follow-up in some studies [100]. The generalizability of these findings is limited because they are mainly based on survivors of assault and traffic accident. Furthermore, although treatment is relatively brief, the applicability of a 5-session treatment following mass trauma events is questionable. Nevertheless, these findings suggest that brief exposure-based interventions delivered early after the trauma accelerate recovery process in survivors and prove effective in preventing chronic PTSD.

				Post-Treatment		Follow-up	
	N conditions	n Treatment	n Control	Effect Size	PTSD diagnosis (Tx vs control)	Effect Size	PTSD diagnosis (Tx vs control)
Acute Stress Disorder							
Brief CBT[1]	4	58	56	1.21	8-13% vs 46-83%	0.83	10-22% vs 22-67%
Imaginal + live exposure[2]	3	54	53	1.13	12-14% vs 56-71%	1.15	15% vs 67%
Cognitive restructuring[3]	1	23	21	0.59	52% vs 71%	--	--
Acute PTSD							
Brief CBT[a, 4]	--	76	76	0.30	30% vs 30%	0.61	10% vs 15%
Brief CBT[5]	--	61	52	0.63	38% vs 61%	0.34	26% vs 44%
Cognitive restructuring + coping skills training[6]	--	10	10	0.82	20% vs 50%	1.03	0 vs 20%

Effect Size = between-groups Cohen's d effect size index

[a] Effect sizes reflect outcome in intent-to-treat analyses.

1 = [99-102], 2 = [23, 103, 147], 3 = [147], 4 = [104], 5 = [148], 6 = [149]

Table 3. Efficacy of brief cognitive-behavioural treatment programmes in ASD and Acute PTSD in randomised controlled trials

Treatment outcome in early intervention studies of acute PTSD was not as good as that obtained in studies of ASD. Table 3 also shows findings from 3 RCTs. These studies are examined separately because their findings were not consistent, probably due to the fact that one study reported only intent-to-treat data. Compared to waiting list groups two studies of brief CBT found only small to moderate treatment effects in PTSD and small effect in depression at both post-treatment and follow-up (conducted about 6 to 13 months post-trauma). More favourable treatment effects were obtained with cognitive restructuring combined with coping

skills training relative to relaxation control, however this study was based on a very small sample.

Interestingly, early interventions produced greater reductions in avoidance behaviour and, whereas significant improvement occurred in reexperiencing and arousal symptoms, negligible reductions occurred on avoidance symptoms in control groups [99, 101-104]. These findings points to the important role played by avoidance symptoms in the maintenance of PTSD. More studies need to be conducted on diverse survivor populations and different cultural settings.

5.3. Propranolol

It has been proposed that the beta-adrenergic antagonist propranolol may have promise in preventing the later development of PTSD by reducing enhancement of traumatic memories. Two RCTs that tested this hypothesis yielded inconsistent results. In one of these studies [105] 41 emergency department patients who had experienced a trauma likely to precipitate PTSD were treated orally with 40 mg of propranolol within six hours of the occurrence of the traumatic event. The drug dose was repeated four times daily for 10 days, with a nine-day taper period. After one month, 18% (2 / 11) of propranolol completers met diagnostic criteria for PTSD, in contrast to 30% (6 / 20) of placebo completers. The drop-out rate from propranolol and placebo was 39% and 13%, respectively. In the other study [106] 48 acute physical injury patients admitted to a surgical trauma centre were randomised to receive propranolol, the anxiolytic anticonvulsant gabapentin, or placebo within 48 hours of trauma. Although well tolerated, neither drug showed a significant benefit over placebo on posttraumatic stress symptoms or depressive symptoms. It is worth noting that 92% of the acutely injured patients refused to participate in the study, in part reflecting their reluctance to receive medication. These inconsistent findings on treatment efficacy considered together with high drop-out rate and refusal to take the medication suggest that medication is not a viable preventative option for PTSD.

6. Conclusion

In this chapter we reviewed critically current treatment approaches for PTSD. The evidence in the literature clearly shows that trauma-focused psychotherapies are the first line of choice in the treatment of PTSD. The question remains as to which trauma-focused treatment protocol is the best option. Exposure therapy involving live exposure and cognitive therapies incorporating an exposure component are the more efficacious treatments for PTSD. Exposure therapy has several advantages over cognitive therapy. Its theoretical background is more robust and experimentally validated than cognitive therapy. It also has larger evidence base, was tested with a wider range of trauma survivors, and has more promise in cross-cultural applicability. Furthermore, cognitive therapy involves elaborate procedures that require substantial training in its administration. Finally, exposure therapy requires relatively less time for observable improvement.

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Despite these advantages exposure therapy is not without problems. About 40% to 50% of patients fail to achieve clinically significant improvement after exposure therapy. These modest improvement rates could be explained by a strong focus on anxiety reduction, rather than anxiety tolerance, which may be counterproductive in treatment. Indeed, the evidence indicates that the degree by which fear reduces or the level of fear following exposure is not related to treatment outcome. Furthermore, exposure therapy is not sufficiently brief for use in mass disaster settings. Although the procedures involved in exposure do not require lengthy and costly training compared to other treatments, they are not suitable for delivery on a self-help basis. There is thus need for a simple and brief intervention that emphasises anxiety / fear tolerance and that can be easily delivered to masses. *Control-Focused Behavioural Treatment* has promise in meeting this need. This short and effective treatment, which emphasizes self-conducted exposure in survivors' daily routine with an aim to increase anxiety tolerance and promote resilience, is suitable for easy distribution to large number of survivors in mass disaster settings.

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Chapter 16

PTSD and the Attenuating Effects of Fish Oils: Results of Supplementation After the 2011 Great East Japan Earthquake

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Evidence of effects of omega-3 polyunsaturated fatty acids on depression and anxiety disorder

Omega-3 polyunsaturated fatty acids (omega-3 PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential fatty acids that cannot be synthesized by humans de novo and must therefore be obtained through the diet. Omega-3 PUFAs are speculated to be beneficial against psychiatric disorders, especially depression, and an increasing growing number of randomized controlled trials (RCTs) have been carried out to verify their efficacy. In fact, a number of previous meta-analyses of RCTs support the positive effects of omega-3 PUFAs supplementation in reducing depressive symptoms [1-7]. However, a recent meta-analysis by Bloch and Hannestad in 2011 found that nearly all evidence of omega-3 PUFAs benefit was removed after adjusting for publication bias [8]. Their meta-analysis has subsequently been criticized by two papers published in quick succession [6, 7]. One of these papers, by Martins et al [6], pointed out methodological flaws with Bloch and Hannestad's analysis. For example, Bloch and Hannestad's analysis included the study examining individuals without formal psychiatric diagnosis, and 2 other studies satisfying their inclusion criteria were not included. Martins et al concluded that supplements containing EPA ≥60% of total EPA + DHA were effective against depression, a finding in agreement with

a meta-analysis by Sublette et al [5]. Taken together, then, the latest evidence does suggest the efficacy of omega-3 PUFAs containing EPA ≥60% against depression.

Several biological mechanisms potentially explain the effect of omega-3 PUFAs in depression and anxiety disorder [1]. To date, however, few RCTs have been carried out to investigate whether omega-3 PUFAs are effective against anxiety disorders. While one such study suggested that omega-3 PUFAs might not be effective for patients suffering from depression with comorbid anxiety disorder [9], some RCTs found that omega-3 PUFAs decreased hostility and aggression among patients with borderline personality disorder [10].

1.2. Omega-3 polyundasurated fatty acids and inflammation

A competitive interaction exists between omega-6 polyunsaturated fatty acids (omega-6 PUFAs) such as arachidonic acid (AA) and omega-3 PUFAs in regard to their shared enzymatic pathways. Compared with the eicosanoids produced from AA, such as prostaglandin E2 (PGE2), those produced from omega-3 PUFAs, such as prostaglandin E3 (PGE3), have little pro-inflammatory activity [11]. Therefore, it is speculated that the amounts of omega-6 eicosanoids released in response to depression-associated inflammation and cell apoptosis, are determined by the fatty acid composition of the cell membrane phospholipids [12]. On this basis, it is thought that increased levels of omega-3 PUFAs in the cell membranes reduces the release of AA-derived prostaglandins, thereby reducing inflammatory activity [13].

Naturally occurring depression-related cell apoptosis may be mediated by free radicals that appear in the brain during the process of inflammatory or ischemic damage. Inflammation and ischemia are known to increase the risk for clinically defined depression [14]. Taken into account that cytokines stimulate the intrinsic pathway of apoptosis and induce depression [15, 16], it is not altogether surprising to find frequent comorbidity of inflammation and depression. The interaction between omega-6 and omega-3 PUFAs eicosanoids, therefore, partly control inflammation, apoptosis and depression as a result [14].

1.3. Omega-3 polyunsaturated fatty acids and neurogenesis

The severity of depression is known to be associated with serum brain-derived neurotrophic factor (BDNF) [17], which exerts various effects on the nervous system, including neuronal outgrowth, differentiation, synaptic connectivity, and neuronal repair and survival [18-20]. Its severity is also associated with low levels of erythrocyte omega–3 PUFAs [21]. Short-term dietary supplementation with omega-3 PUFAs has been shown to up-regulate adult neurogenesis in lobsters [22]. In rats, dietary omega-3 PUFAs increased levels of BDNF, which promotes neuronal survival and growth [23].DHA extended neurites and branches of rat hippocampal neurons in vitro [24]. DHA supplementation to rats also promoted the maturation of neurons and hippocampal neurogenesis in vivo [25].. On the basis of these findings, omega-3 PUFAs supplementation can enhance the effect of BDNF-related synaptic plasticity and neurogenesis.

Additionally, in PTSD, the pathogenesis of which is characterized by excess consolidation of fear memory and failure of extinction learning [26], it might be possible to control fear memory

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by regulating hippocampal neurogenesis [27]. Indeed, in mice with active hippocampal neurogenesis, the period of hippocampus-dependent fear memory was found to be shorter [28]. Given the findings of animal research conducted to date, omega-3 PUFAs seem to be the most promising candidate for dietary intervention to facilitate adult hippocampal neurogenesis following a traumatic event [25, 29]. In fact, in an open label trial in patients with physically injury, we previously found that PTSD symptoms were significantly alleviated by taking DHA-rich fish oil [30].

1.4. Background of the study

On March 11, 2011, The Great East Japan Earthquake and tsunami devastated the northeastern coast of Japan. As of July 18th, 2012, 15,867 died and 2,906 were missing arrocding to the National Police Agency. Many rescue workers, as well as survivors, were exposed to traumatic experiences. A number of studies have reported adverse psychological outcomes among rescue workers. In a study of medical care personnel sent to aid trauma victims of an airline crash, 13.5% developed PTSD within 18 months of the crash [31]. Similarly, in a study of rescue workers deployed to the site of the September 11 terrorist attack in New York in 2001, 16.7% developed PTSD and 21.7% developed depression at 13 months after the attack [32]. Moreover, peritraumatic distress (distress during and right after a traumatic experience) and TV viewing for extended periods were shown to predict PTSD symptoms in rescue workers [33, 34]. PTSD is associated with higher psychiatric comorbidity, attempted suicide, and physical illnesses [35], as well as with high medical expenses [36]. An appropriate strategy for the prevention of PTSD in rescue workers is therefore clearly required, but as yet adequate measures have not been developed.

Against this background, we carried out a study to determine whether fish oil supplementation can attenuate PTSD symptoms among rescue workers after the Great East Japan Earthquake. The main findings have been breifly reported elsewhere [37] and here we present the overall findings of the study.

2. Methods

2.1. Participants

This trial named "Attenuating posttraumatic distress with omega-3 polyunsaturated fatty acids among disaster medical assistance team members after the Great East Japan Earthquake (APOP)" was a single-blind, randomized, parallel-group field trial administered by the National Disaster Medical Center (NDMC), Tokyo, Japan. The head office of the Disaster Medical Assistance Team (DMAT) is located at NDMC. DMAT members are doctors, nurses, and operational coordination staff (medical or clerical staff who are neither doctors nor nurses) who are dispatched as a mobile medical team with specialized training that is capable of acting during the acute phase of a large-scale disaster. DMAT activities commenced on the day of the Great East Japan Earthquake, March 11, and concluded on March 22.

The DMAT members recruited to the present trial met the following inclusion criteria: 1) aged 18 years or older; 2) a native Japanese speaker or non-native speaker with Japanese conversational abilities; and 3) physically and psychologically capable of understanding and providing consent for study participation. The exclusion criterion was regular intake of warfarin for at least 3 months before deployment, because Fish oil supplementation could have provided additional anticoagulation with warfarin.

2.2. Procedures

The detailed trial procedures have been reported elsewhere [38], but briefly a written guide to the study, including an explanation of the study and informed consent, was posted to the Emergency Medical Information System by DMAT head office and a mass email was sent to all DMAT members asking for their participation. The Peritraumatic Distress Inventory (PDI) [39, 40] was used to quantify peritraumatic distress. Other detailed baseline assessment has been reported elsewhere [38].

2.3. Ethics

The study protects the rights and welfare of participants in the spirit of ethical guidelines outlined under the Declaration of Helsinki, and further respects the ethical principles of the Ministry of Health, Labour, and Welfare of Japan. The study was approved by the Ethics Committee of the NDMC on April 1, 2011. Individual participants in this study gave written informed consent.

2.4. Interventions

For participants allocated to the fish oil plus psychoeducation group, seven capsules per day, each containing 320 mg of fish oil, were provided in line with previous research [41]. The fish oil composition of each capsule was 70% DHA and 7% eicosapentaenoic acid (EPA). Each capsule was placed in a brown 500-ml polyethylene container with a wide opening. Participants were instructed to take the capsules after eating and additionally told that they might take a full day's dosage at one time. For participants of both groups, a leaflet on psychoeducation about posttraumatic distress focusing on critical incident stress was provided.

2.5. Objectives

This study aimed to determine whether fish oil supplementation can attenuate the symptoms of PTSD and other posttraumatic distress such as depression among DMAT workers who were deployed during the acute disaster phase of the Great East Japan Earthquake.

2.6. Outcomes

The primary outcome was total score on the Impact of Event Scale-Revised (IES-R) at 12 weeks after shipment of the supplements on April 19, 2011. The IES-R, developed by Weiss, is a self-reporting questionnaire about PTSD symptoms and is the most widely used measure internationally in all forms of disaster-area research [42]. The IES-R is composed of 22 items on the

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three largest symptoms in the diagnostic criteria of PTSD, namely re-experiencing, avoidance, and hyperarousal. Respondents rate symptoms experienced in the previous week. The validity and reliability of the Japanese version of the IES-R has been confirmed [43].

Secondary outcomes were the total scores on each of the Kessler 6 Scale, the Center for Epidemiologic Studies Depression Scale (CES-D), and the shortened 14-item version of the Resilience Scale at 12 weeks after shipment of the supplements. the Kessler 6 Scale, developed by Kessler et al. [44], is a self-reporting questionnaire designed to screen for psychiatric disorders and mood and anxiety disorders; the CES-D, developed by Radloff [45], is a self-reporting questionnaire on depression; and the shortened 14-item version of the Resilience Scale, developed by Wagnild and Young [46], is a self-reporting questionnaire for quantitative evaluation of resilience. The Japanese version of each of these three scales has been validated [47-49].

Safety of the intervention was evaluated by the presence of adverse events during the observation period, by asking the participants about the presence of such events at 2, 4, 8, and 12 weeks after the start of fish oil supplementation. Whenever inquiries were received from participants, necessary information was provided to them.

2.7. Sample size

We estimated that the mean improvement in IES-R score as the primary outcome measure would be 10 (SD 15) for the fish oil plus psychoeducation group and 0 (SD 15) for the psychoeducation alone group [30]. We set α level at.05 and β at.10. This brought us to our required sample size estimation of 48 cases per group. Because the control group in this study received psychoeducation, we allowed up to 150 cases for the intervention group and 300 cases for the control group.

2.8. Randomization

Participants were randomly assigned to either the fish oil supplementation plus psychoeducation group or psychoeducation alone group. The trial statisticians (NN and TS) independently conducted randomization by the permuted block method using a four-person block, and concealed allocation mechanism until the study was finished. The participants were stratified by sex because previous studies showed that the prevalence of PTSD and of major depressive disorder was higher in women than in men [50].

2.9. Blinding

Because placebo capsules were not provided to psychoeducation alone group, participants could not be masked. Also, the researcher who provided necessary information regarding safety management to the participants (DN) could not be masked in just a few cases when participants inadvertently stated that they took the fish oils capsules. Other researchers were masked to allocation.

2.10. Statistical methods

All analyses were conducted according to the intention-to-treat principle. A sensitivity analysis was performed using a multiple imputation procedure with SAS version 9.1 (SAS Institute Inc, Cary, North Carolina) to impute each psychological variable end point for participants who did not have a follow-up psychological variable assessed.

Analysis of covariance (ANCOVA) was used to investigate the significance of the differences in the initial values as well as those of the net changes after the intervention among the 2 groups, 95% confidence interval values, and P values. Covariates for ANCOVA were sex, age, and each psychological variable score at baseline. In addition, we examined the impact of sex difference for fish oil supplementation on posttraumatic distress. A two-tailed test was used, with the α level set at 0.05.

3. Results

3.1. Participants flow and recruitment

Figure 1 shows the trial profile. Of the 1,816 DMAT workers deployed to the disaster areas, 172 were enrolled and randomly allocated to the fish oil plus psychoeducation group or psychoeducation alone group between April 2 and 12, 2011 (Figure 1). The mean duration from baseline assessment to follow-up assessment was 14.2 weeks (SD 0.9), and from shipment of the supplements to follow-up assessment was 12.6 weeks (SD 0.8). Only 1 participant in the psychoeducation alone group was lost to follow-up.

3.2. Baseline data

The two groups were well balanced with respect to baseline characteristics, except that the IES-R total and intrusion subscale scores were relatively high in the intervention group (Table 1). The mean term of the deployment was 4.1 days (SD 2.0). Two participants (1%) were injured during deployment, 11 (6%) saved children, 24 (14%) had contact with corpses, and the median of the PDI was 12.5 (range 0-42). These variables, identified as risk factors for PTSD in previous research [31, 51], did not differ significantly between the two groups. The PDI scores were comparable to those in accident survivors (Median 15.0, range 0-40] [52, 53].

3.3. Numbers analyzed

Eighty-six participants were assigned to each group. Primary outcome data were available for all participants, except one. All participants constituted the intention-to-treat population. The imputation technique assigned changes in the effectiveness end point for the noncompleter based on the participant's baseline characteristics and baseline psychological variables.

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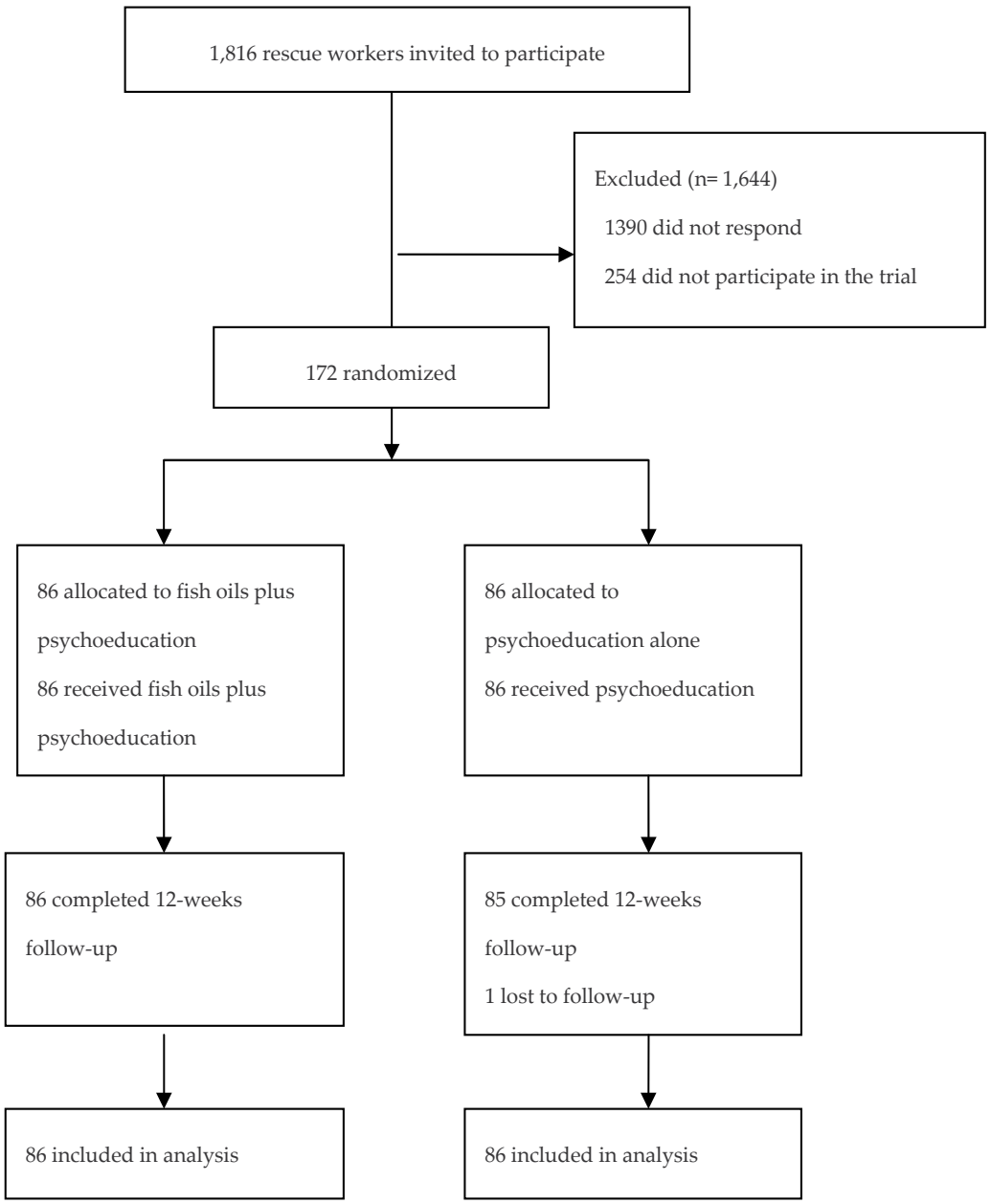

Figure 1. Flow diagram of the study

	Fish oil plus psychoeducation group (n=86)	Psychoeducation alone group (n=86)	P value*1
Demographic data			
Age in years (mean±S.D.)	37.9 ± 7.4	37.4 ± 7.4	0.62
Women (%)	27.9	26.7	0.86
BMI (mean±S.D.)	22.7 ± 2.8	23.0 ± 3.0	0.50
Occupation (%)			0.87
Medical Doctor	26.7	24.4	
Nurse	46.5	45.4	
Other	26.7	30.2	
Years of occupational experience (mean±S.D.)	14.5 ± 7.2	13.2 ± 7.3	0.24
Previous disaster operation experience (%)	27.9	26.7	0.86
Married (%)	67.4	72.1	0.51
Has a child (or children) (%)	57.0	61.6	0.53
Education (%)			
University or higher	47.7	53.5	0.45
Current smoker (%)	29.1	23.3	0.39
Current drinker (%)	80.2	83.7	0.55
Has past history of any physical disaeses*2 (%)	0.0	0.0	-
Has past history of depression (%)	0.0	4.7	-
Psychological data			
IES-R (mean±S.D.)			
IES-R-Total	14.5 ± 15.1	10.7 ± 11.5	0.07
IES-R-Intrusion	6.5 ± 6.6	4.7 ± 5.1	0.05
IES-R-Avoidance	4.0 ±5.2	3.0 ± 4.2	0.16
IES-R-Hyperarousal	3.9 ± 4.6	2.9 ± 3.6	0.12
K6 (mean±S.D.)	4.5 ± 5.0	3.4 ± 4.2	0.13
CES-D (mean±S.D.)	13.6 ± 9.1	11.6 ± 8.1	0.13
RS-14 (mean±S.D.)	65.5 ± 10.3	67.1 ± 9.9	0.31

Abbreviations: IES-R, Impact of Event Scale-Revised; K6, Kessler 6 Scale; CES-D, Center for Epidemiologic Studies Depression Scale; RS-14, Resilience Scale 14-item version

*1) Student's t test or Chi-square test

*2) Physical disease defined as cancer, cardiovascular disease, stroke, chronic renal disease, chronic liver disease, and accidental injury.

Table 1. Characteristics of the study population at randomization

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3.4. Outcomes and estimation

ANCOVA adjusted for sex and age showed a significant reduction in IES-R intrusion and hyperarousal subscale scores in the fish oil plus psychoeducation group. When adjusted for the scores at baseline, however, no significant difference in primary outcome was seen between the two groups when adjusted for the scores at baseline (-0.9, 95% CI, -3.0 to 1.2; P = 0.39) and no significant differences were seen in any of secondary outcomes (Table 2).

Variables	Baseline (mean±S.D.)	After 12 weeks (mean±S.D.)	Net change 1 (95% CI)	P value	Net change 2 (95% CI)	P value
IES-R-Total						
Fish oils group	14.5 ± 15.1	9.0 ± 9.5	-2.7	0.06	-0.9	0.39
Control group	10.7 ± 11.5	7.9 ± 10.0	(-5.5, 0.1)		(-3.0, 1.2)	
IES-R-Intrusion						
Fish oils group	6.5 ± 6.6	3.3 ± 3.4	-1.5	0.03	-0.5	0.28
Control group	4.7 ± 5.1	3.1 ± 3.7	(-2.8, -0.2)		(-1.3, 0.4)	
IES-R-Avoidance						
Fish oils group	4.0 ± 5.2	3.3 ± 4.4	-0.04	0.94	0.3	0.44
Control group	3.0 ± 4.2	2.4 ± 3.7	(-1.0, 0.9)		(-0.5, 1.1)	
IES-R-Hyperarousal						
Fish oils group	3.9 ± 4.6	2.3 ± 2.7	-1.1	0.03	-0.6	0.11
Control group	2.9 ± 3.6	2.5 ± 3.5	(-2.1, -0.1)		(-1.4, 0.1)	
K6						
Fish oils group	4.5 ± 5.0	2.9 ± 3.4	-0.4	0.52	0.2	0.62
Control group	3.4 ± 4.2	2.2 ± 3.7	(-1.5, 0.8)		(-0.6, 1.1)	
CES-D						
Fish oils group	13.6 ± 9.1	10.8 ± 6.3	-1.5	0.20	-0.3	0.73
Control group	11.6 ± 8.1	10.3 ± 7.2	(-3.9, 0.8)		(-2.1, 1.5)	
RS-14						
Fish oils group	65.5 ± 10.3	67.2 ± 11.3	2.7	0.09	2.2	0.15
Control group	67.1 ± 9.9	66.1 ± 13.3	(-0.4, 5.8)		(-0.8, 5.2)	

Abbreviations: IES-R, Impact of Event Scale-Revised; K6, Kessler 6 Scale; CES-D, Center for Epidemiologic Studies Depression Scale; RS-14, Resilience Scale 14-item version; CI, confidence interval

Net change 1: Analysis of covariance (ANCOVA) adjusted for sex and age

Net change 2: Analysis of covariance (ANCOVA) adjusted for sex, age and each psychological variable score at baseline

Table 2. Change in IES-R, K6, CES-D and RS-14 scores of participants in the fish oils and control groups

Because previous studies showed that the prevalence of PTSD and of major depressive disorder was higher in women than in men [50], subgroup analysis by sex was pre-specified. In women, the IES-R total mean score was reduced from 15.7 (SD 14.9) at baseline to 9.3 (SD 8.8) at follow-up in the fish oil plus psychoeducation group, compared to that from 11.2 (SD 13.0) to 10.4 (SD 12.3) in the psychoeducation alone group. In men, the IES-R total score was reduced in both groups, from 14.0 (SD 15.3) to 8.9 (SD 9.9) in the fish oil plus psychoeducation group and from 10.5 (SD 11.1) to 6.9 (SD 9.0) in the psychoeducation alone group. Remarkably, even when adjusted for age and IES-R scores at baseline, change in the IES-R score of women in the two groups from baseline to 12weeks was -3.9 (95% CI, -7.5 to -0.3; P = 0.04) (Table 3).

Regarding adherence, 7 out of 86 participants (8%; 6 male, 1 female) in the fish oil plus psychoeducation group took fish oil supplements 2 days or less per a week.

3.5. Adverse events

The occurrence rate of adverse events was not significantly different between the two groups, with 32 participants (37%) in the fish oil plus psychoeducation group reporting at least one adverse event versus 22 (26%) of the psychoeducation alone group doing so. Of these events, none were regarded as serious or led to withdrawal. The main adverse events included loose bowel (21 (24%) in the fish oil plus psychoeducation group versus 15 (17%) in the psychoeducation alone group) and belching (12 (14%) in the fish oil plus psychoeducation group versus 7 (8%) in the psychoeducation alone group).

4. Discussion

4.1. Interpretation

This trial regretfully did not show the superiority of fish oil supplementation plus psychoeducation over psychoeducation alone for the prevention of PTSD and depressive symptoms among rescue workers. Even though a relatively good improvement was seen in IES-R score in the fish oil plus psychoeducation group, the improvement did not reach statistical significance. Furthermore, we recorded no significant differences between the two groups for the 3 secondary outcomes.

One of the possible reasons for not detecting the effectiveness of fish oil supplementation was that posttraumatic distress was reduced in both groups. A previous study of disaster workers at the September 11 terrorist attack sites showed that depressive symptoms were increased from 7 months after the disaster to 13 months after, while PTSD symptoms were reduced from 1 week to 13 months afterward [32]. In the present study, all psychological variables were reduced to some extent in both groups. Participants in both groups were contacted at 2, 4, 8, and 12 weeks for safety management and necessary information was provided to them upon request for ethical reasons: such contact might have been supportive for both groups of participants. Psychoeducation provided before the baseline assessment also might affect the results.

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Variables		Net change (95% CI)	P value
IES-R-Total			
	Women	-3.9 (-7.5, -0.3)	0.04
	Men	0.2 (-2.2, 2.7)	0.86
IES-R-Intrusion			
	Women	-1.3 (-2.9, 0.4)	0.12
	Men	-0.1 (-1.1, 0.8)	0.78
IES-R-Avoidance			
	Women	-0.4 (-1.9, 1.1)	0.58
	Men	0.6 (-0.4, 1.6)	0.23
IES-R-Hyperaruosal			
	Women	-1.9 (-3.4, -0.5)	0.009
	Men	-0.1 (-1.0, 0.8)	0.77
K6			
	Women	0.1 (-1.9, 2.1)	0.90
	Men	0.2 (-0.7, 1.2)	0.61
CES-D			
	Women	-2.8 (-6.4, 0.8)	0.13
	Men	0.5 (-1.5, 2.6)	0.60
RS-14			
	Women	3.7 (-1.5, 9.0)	0.16
	Men	1.7 (-2.0, 5.4)	0.36

Abbreviations: IES-R, Impact of Event Scale-Revised; K6, Kessler 6 Scale; CES-D, Center for Epidemiologic Studies Depression Scale; RS-14, Resilience Scale 14-item version; CI, confidence interval

Net change: Analysis of covariance (ANCOVA) adjusted for age and each psychological variable score at baseline

Table 3. Change in IES-R, K6, CES-D and RS-14 scores of participants in the fish oils and control groups stratified by sex

The fish oil capsules used in this study contained 1,568 mg DHA and 157 mg EPA per day. Based on previous studies [25, 29], DHA rather than EPA appeared to facilitate adult hippocampal neurogenesis. However, there is evidence to support the effectiveness of EPA monotherapy or a combination of EPA and DHA for depressive disorders [1]. A recent review showed that a 2:1 EPA:DHA ratio might be optimal for the treatment of depressive disorders [54]. In fact, our open label trial in physically injured patients failed to alleviate depressive symptoms, while alleviating PTSD symptoms [30]. To our knowledge, no previous studies have examined the effectiveness of fish oils to prevent PTSD. The appropriate composition of fish oil capsules to prevent PTSD warrants attention.

Remarkably, fish oil supplementation plus psychoeducation significantly lowered the IES-R total and hyperarousal subscale scores in women, despite the small sample size of women. To our knowledge, this is the first randomized controlled trial to show that fish oil reduced PTSD symptoms in women. While this outcome could be caused by chance because this was a secondary analysis, our finding coincides with that of previous longitudinal studies in Finland, Spain, and the United States [55-57] showing dietary intake of fish decreased the risk of developing depression in women, but not in men. Moreover, in Japan, a very low intake of fish was found to be associated with increased risk of suicidal death in women [58]. Although the difference in depressive symptoms assessed by the CES-D did not reach statistical significance among women in the present study, further studies with a large sample size may prove the effectiveness of fish oil supplementation for attenuating depressive symptoms in women. Also, our finding that women who took the fish oil supplements had a significant reduced score on the hyperarousal subscale is also partly consistent with a previous study showing that DHA intake prevented aggression from increasing at times of mental stress [41]. It is unclear why fish oils play an important role for regulating psychological well-being only in women, but it could be explained by the fact that estrogens cause higher DHA concentrations in women than in men [59]. Future studies should determine the effect of the sex difference in the effectiveness of fish oil supplementation for PTSD and posttraumatic depressive symptoms.

In addition to the possibility that fish oils do attenuate PTSD symptoms in women, it is well known that fish oils are effective for the secondary prevention of cardiovascular disease. An ecological study revealed that the availability of omega 3 PUFAs was inversely related with disease rates in 12 risk models, such as mortality from stroke and cardiovascular disease, as well as depression [60]. Given these positive effects on physical health and low rates of severe adverse events, fish oil supplementation could be a safe and novel strategy for the prevention of PTSD in women.

4.2. Generalizability

As shown in the figure 1, 1,390 out of 1,816 rescue workers invited to participate did not respond, which could limit the external validity of the findings. This might be because many rescue workers committed themselves to important roles at their own hospitals immediately after their deployment and could hardly afford to participate in this study.

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4.3. Limitations

This study has some strengths. The participants are representative of all DMAT workers in that they are based across Japan. Baseline assessments were conducted within 1 month after the earthquake, which would minimize recall bias, and the attrition rate (<1%) was extremely low.

However, the study also has some limitations. First, this study was not a placebo controlled, double-blind trial. Because this study was implemented at a time of crisis, we could not prepare placebo capsules. It might be possible that we found a placebo effect acted more strongly in women who took the fish oil supplements. We are currently implementing a double-blind, placebo control trial of fish oils for the prevention of PTSD in physically injured patients (ClinicalTrials.gov Identifier: NCT00671099]. Second, this study relied on self-reports of adherence to the protocol, rather than biomarkers. We are currently measuring fatty acid composition of red blood cell membranes in a double-blind controlled trial mentioned above. Third, the finding of efficacy for women is driven by the significant reduction in hyperarousal cluster symptoms. Hyperarousal cluster symptoms are not PTSD-specific and are similar to the symptoms of other anxiety and mood disorders. Because assessment of PTSD is a self-report screening instrument rather than a structural interview, this study could not rule out an alternative explanation of the positive finding for women that attributes that difference to changes that are not related to PTSD.

5. Conclusion

This trial did not show the effectiveness of fish oil supplementation for the prevention of PTSD and depressive symptoms in rescue workers. However, the supplements did reduce PTSD symptoms significantly in women. Due to limitations mentioned above, the result of this study is a preliminary and should be accepted cautiously, but at the same time it is an encouraging finding. Not only rescue workers but large numbers of people were traumatized by natural disasters such as the Great East Japan Earthquake, and psychiatric resources to support them have been limited. Against this background, daily life-based intervention for the prevention of PTSD is preferable. Fish oil supplementation may offer a safe strategy for preventing PTSD in women, and thus is an important topic that should be further explored in disaster mental health care.

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Chapter 17

New Approaches to the Psychological Treatment of Obsessive-Compulsive Disorder in Adults

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Additional information is available at the end of the chapter

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1. Introduction

The key features of Obsessive-Compulsive Disorder (OCD) are the experience of recurrent, unwanted and intrusive thoughts (obsessions) and/or the completion of repetitive ritualistic behaviours (compulsions). Compulsions are frequently performed to reduce the distress associated with the obsessional thoughts [1]. The lifetime prevalence of OCD is estimated to be 2-3% in the general population, with epidemiological studies indicating consistency in rates across different countries and cultures [2,3].

OCD is a severe anxiety disorder that is associated with significant disability. In fact, the World Health Organisation has rated OCD as the tenth leading cause of disability in the world. If left untreated, OCD typically becomes a chronic problem with a pattern of frequent re-occurrence and relapse [2]. Unfortunately, many individuals will significantly delay help-seeking, due to reasons such as a fear of embarrassment, and thus suffer for years with significant symptoms and distress [4,5].

OCD is typically diagnosed according to Diagnostic and Statistical Manual of Mental Disorders criteria [1]. These stipulate that the individual must experience either obsessions, compulsions, or both, and that these must interfere with the individual's life due to the time they consume (i.e., more than one hour per day) or by causing marked distress or significant impairment. To obtain an accurate diagnosis, clinicians will often use structured diagnostic interviews such as the Mini International Neuropsychiatric Interview (MINI) [6], Anxiety Disorders Interview Schedule (ADIS-IV) [7], or Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID) [8]. Furthermore, clinicians and researchers will frequently utilize a selection of measures to ascertain symptom severity and to assess for clinical outcomes. The most common of these include the Yale-Brown Obses-

sive Compulsive Symptom Checklist (YBOCS) [9], and the Obsessive Compulsive Inventory – Revised (OCI-R) [10].

2. Why new approaches to treatment are needed

For some time now, the dominant approach to treating this disorder is a behavioural therapy called Exposure and Response Prevention (ERP). ERP is considered the gold-standard treatment as it currently has the most convincing evidence of efficacy from several controlled trials [11] and metaanalytic studies [12] spanning a number of years. In a study examining the change scores as a result of treatment outcomes, Fisher and Wells [13] found that 50-60% of participants were likely to be classified as recovered following ERP treatment. ERP is typically delivered on an individual basis and may be implemented as a stand alone treatment, or combined with cognitive strategies under the label of Cognitive Behaviour Therapy (CBT). Despite the success of ERP in alleviating the symptoms of OCD for many individuals, there remains much scope for further improving the success of psychological treatments for the disorder. Issues such as treatment refusal, non-completion of ERP, non-response in some cases and restricted accessibility are just some problems effecting outcomes.

Presently, there are major issues with costs and limited psychological therapy resources in the public healthcare system [14]. There are very limited therapeutic services available to the public in the area of OCD, and the majority of individuals do not have access to good treatments. According to Shafran and colleagues [15], evidence suggests that even though a number of evidence-based psychological treatments have been developed, clients are not receiving them within clinical settings. Furthermore, when evidence-based psychological treatments are delivered, they are often not delivered to an optimal standard [15]. Shafran and colleagues [15] provided a number of recommendations to approach this gap in well-delivered evidence-based psychological treatments, however, it may take time to increase awareness and knowledge about evidence-based psychological treatments, as well as the implementation of them. Given the lack of available therapeutic services being provided to the public as well as the delivery of evidence-based psychological treatments, a stepped care approach could provide another solution in the meantime to this problem [14].

A stepped care approach simply refers to treatments at differing intensities [14]. Within a stepped care approach, the treatment must be the least restrictive, but still provide significant improvements to health. With this in mind, if a treatment is provided at a lower level or step, and the client is not improving post-treatment, the client's needs should be evaluated, and an appropriate step to treatment provided. The restrictiveness of a treatment generally refers to the cost and personal inconvenience. When referring to the therapist, it can also refer to the availability of the therapists time and the amount of time required by a specialist therapist [14]. Given the limited number of therapists trained in the area of OCD, a stepped care approach appears to be particularly warranted in the treatment of OCD.

The National Institute for Health and Clinical Excellence (NICE) Guidelines for Obsessive-compulsive disorder [16], a world-renowned document outlining evidence-based ap-

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proaches to treating the disorder, endorses the use of a stepped-care model in the prevention and provision of treatment services to individuals with OCD. The NICE Guidelines outline six levels of intervention as follows. It should be noted that all references to CBT within this stepped care model emphasize the need to include an ERP component in therapy.

Step 1: Awareness and recognition

Step 2: Recognition and assessment (including referral to appropriate services)

Step 3: Initial treatment by guided self-help and CBT via group or individual format

Step 4: For OCD with comorbidity or a poor response to initial treatment - treatment via CBT within a multidisciplinary team, possible medication

Step 5: For OCD with significant comorbidity, severe impairment or limited treatment response - specialist treatment services with expertise in CBT, possible medication

Step 6: Inpatient or intensive treatment programs including medication and CBT to reduce the risk to life, severe self-neglect or severe distress or disability.

As can be seen, while the higher level steps within this care model indicate the need for ERP based psychotherapy, which is provided on an individual basis, there is much scope for exploring less intensive, less costly, and more widely accessible formats for the delivery of ERP based treatment programs.

Furthermore, it is important to review emerging and alternate approaches to the conceptualization and treatment of this disorder. The capacity for ERP based treatments to bring about considerable and clinically significant change for many clients is well documented. However, prior studies have noted that up to 25% of patients refuse ERP treatment due to the time commitments needed to complete the treatment, a fear that the exposure exercises will bring about overwhelming anxiety, or a fear that a dreaded outcome will occur should the individual fail to complete their rituals [17]. Within this stepped care model there are limited evidence-based alternatives for treatment other than medication-based treatment, which individuals may also refuse or be unable to tolerate. It is therefore important that we continue to explore new psychological treatment approaches for this disorder and thus offer hope to those who refuse or do not respond to the current gold-standard treatment approaches.

3. New Treatment Approaches

The following section will provide a review of a number of new approaches to the treatment of OCD. First, the use of treatment modalities that differ from standard individual based CBT or ERP will be discussed. This will explore the use of the group therapy format, and the use of modern technologies in the delivery of cognitive and behavioural therapies. Next, emerging conceptualizations and treatment approaches will be discussed. This will review the evidence for Metacognitive and Acceptance and Commitment based approaches to the management of OCD. Each approach will first be described, the proposed mechanisms of change outlined and then a critical review of the evidence for efficacy will be offered.

Group therapy for OCD

The predominant groups that have been evaluated for OCD are either cognitive, behavioural or a combination of both. Provision of therapy in groups for OCD makes intuitive sense because of the known issues relating to shame, isolation and embarrassment that have been identified amongst sufferers. Being able to meet others with a similar set of problems can allow for symptoms to be normalized and destigmatised. Participating in a group can allow the individual to develop a support network for sharing strategies, information and resources, and the process of helping others may enhance ones self-esteem, and sense of social competence and connectedness. From a clinical perspective, peer modeling of ERP exercises may provide additional opportunities for exposure and reinforce compliance with homework. In addition to these potential advantages, as already mentioned, stepped-care models emphasize the importance of providing treatment options which are less costly and intensive. Group therapy formats have the capacity to increase access to well-trained clinicians, and decrease potential waiting times.

Empirical Evidence for Group CBT for OCD

A meta-analysis by Jónsson and Hougaard [18] examined the effectiveness of group CBT and ERP as reported in thirteen prior treatment trials. This included randomized controlled trials, non-randomized controlled trials, and naturalistic trials. The meta-analysis indicated that group CBT and ERP yields a large overall pre-post effect size of 1.18. Importantly, group dropout rates of 13.5% were compared with reported individual treatment dropout rates of 12.1%. This was considered an indication that the group format seemed an acceptable method of treatment delivery to most patients. When this information is combined with the earlier findings that direct comparisons between group and individual based treatments have not demonstrated a significant difference in post treatment outcomes [19,20], group CBT and ERP certainly appear to be viable and efficacious treatment options in the management on this disorder. Furthermore, the meta-analysis indicated that compared to pharmacological treatment, the between groups effect size of 0.80 favoured group CBT/ERP.

Since this meta-analysis, Belotto-Silva and colleagues [21] compared group CBT (GCBT) with Fluoxetine, a Selective Serotonin Reuptake Inhibitor, in a controlled trial including 158 participants (GCBT N=70; Fluoxetine N=88). A total of 12 group therapy sessions of 2 hours duration were provided each week. The Fluoxetine group received 80mg/day for the same duration (12 weeks). Mean YBOCS scores decreased by 23% (GCBT) and 21% (Fluoxetine). The authors note that this level of symptom reduction, although significant, is less than has been observed in some other CBT studies. They conclude that this is most likely due to the high rate of comorbidity present in the sample. In fact the results are closer to other similar studies that have utilised less stringent exclusion criteria and therefore arguably more representative samples [19,22]. In another study since the meta-analysis [23], the effectiveness of GCBT for OCD was further evaluated in a representative, clinic sample in Norway. In this open trial, 54 patients diagnosed with OCD were provided with 12 sessions of GCBT. At post treatment and again at 3 and 12 month follow-up significant improvements in OCD symptoms as well as depression and anxiety were observed.

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It could be argued that these outcomes are simply due to the non-specific effects of participating in a group, such as the increased social support that participants experience. A study by Fineberg and colleagues [24] therefore attempted to account for the role of non-specific group effects within their research design by including a relaxation placebo control group. The outcomes indicated that both those in the CBT and relaxation placebo group improved, and that there was no significant difference between the outcomes for the two groups. However, there was a significant bias towards non-uptake of the relaxation therapy condition. With more potential participants dropping out prior to the trial even beginning, this may mean that the final relaxation group participants represented individuals predisposed to believe that relaxation was a credible form of treatment for OCD and that they therefore had enhanced expectations of treatment. There was also a significant difference in drop-out rates across conditions with 35% of participants dropping out of the relaxation group compared to 4% in the CBT group. Due to the observed difficulties with finding a credible group placebo, we are not yet able to ascertain whether these results are simply due to the non-specific group factors. However, this study yielded a large treatment effect size of 1.45 for GCBT, providing further support for the further use of group CBT.

Overall, the large effect sizes noted in prior studies demonstrate that group CBT and ERP are viable treatment options for service provision, with comparable findings to individual therapy and pharmacological treatments for OCD. Although further group placebo controlled trials may go some way to separating out the effects of non-specific group factors, the consistent reports of clinically and statistically significant improvements for participants, and the potential improved access to expert services for clients and cost savings for clinicians indicate that group therapy is a worthy option in the treatment of this disorder.

Telemental Health Approaches

Telemental health is a term used to capture the broad application of telecommunication and information technology in the provision of various mental health services. There are a number of different applications that have been developed and trialed for the treatment of OCD in adults. A summary of the evidence base and key advantages and disadvantages of these applications is provided in Table 1.

	Evidence	Decreases physical barriers to treatment	Improves access to expert clinicians	Impact on time required	Other potential advantages	Other potential disadvantages

				of clinician		
Telephone-based						
No therapist (automated)	RCTs	Yes	No	Eliminates	Able to be completed at time selected by client	Isolation, lack of therapeutic alliance may impact on treatment adherence and retention
With therapist	RCTs	Yes	Yes	Decreases	Regular contact may improve treatment compliance, support for clients experiencing difficulty with program	Lack of non-verbal cues
Video-conferencing	Case series	Yes	Yes	No change	Able to be conducted on mobile devices and home computers, presence of non-verbal cues, observation of exposure exercises	Observation of non-verbal cues may be limited by screen set-up, clients may not be familiar or comfortable with technology
Internet-based						
No therapist	Open trial	Yes	No	Eliminates	Able to be completed at time selected by client	Isolation, lack of therapeutic alliance may impact on treatment adherence and retention
With therapist	Open trial	Yes	Yes	Decreases	Regular contact may improve treatment compliance, support for clients experiencing difficulty with program	Lack of non-verbal cues
Virtual Reality	Case series	Yes	No	Decreases	Technology may enable treatment to be conducted on mobile devices and home computers	Virtual environment may not extend to cater for idiosyncratic presentations

Table 1. Advantages and disadvantages of telemental health approaches

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Telephone-Based Treatments

BT-Steps [25] is a well-evaluated behaviour therapy self-help program that is administered via the telephone. It does not involve direct therapist contact as clients simply access an automated system where they enter details of their progress and receive automatic suggestions and prompts from an electronic recording. Reductions in YBOCS symptoms of up to 30% have been reported in open studies of patients who completed the self-exposure phase of BT-Steps [26] however a major limitation of this approach is the unusually high dropout rate that has been observed in the studies. In attempt to investigate this further, Kenwright, Marks, Graham, Franses and Mataix-Cols [27] compared the self-administered BT-Steps to a BT-Steps with inclusion of nine sessions of therapist support. Those in the supported condition evidenced both improved compliance and outcomes.

Three trials of CBT via telephone with therapist contact have been conducted with increasingly improved methodological rigor. Lovell and colleagues [28] first conducted a case series with four participants examining the impact of eight weekly telephone contacts with a cognitive behavioural therapist, starting and ending with a face-to-face session. Three out of the four participants improved, with reductions of between 24% to 67% noted on the YBOCS. In a later trial, Taylor and colleagues [29] provided 12 weekly therapy sessions by phone and with provision of a self-help book and compared this to a waitlist control. Thirty three participants were included and results indicated significant reduction in symptoms for the telephone group. More recently, Lovell and colleagues [30] compared telephone-based treatment with face-to-face CBT in a non-inferiority trial involving 72 participants. In each condition participants received 10 therapy sessions however, the telephone sessions were half the duration of the face-to-face sessions. Equivalent improvements were found across both groups suggesting that the telephone condition may represent an effective treatment with considerable reduction in therapist's time requirements.

Videoconferencing

Videoconferencing is a computer-assisted approach that bears the closest resemblance to face-to-face therapy because both therapist and client interact in real-time. It has major advantages in terms of eliminating the issue of distance between therapist and client. It is particularly beneficial for clients who have restricted mobility for any reason or who might not otherwise be inclined to leave their homes to attend therapy sessions. To date, two studies have explored the treatment of OCD via videoconference. Himle and colleagues [31] utilised a multiple-base line design to analyse the outcomes of a 12-week manualised CBT intervention. Three participants were included in the study and significant improvements in symptoms were observed for all participants as measured by the YBOCS. Participants also reported high satisfaction with the therapy and excellent scores on therapeutic alliance were also obtained.

In a recent case series design, Vogel and colleagues [32] investigated the effectiveness of videoconferencing therapy with the addition of cell phones. Fifteen sessions of ERP was delivered via six teleconference and nine cell phone sessions. Four of the six participants made substantial gains and no longer met criteria for OCD at the end of therapy. Importantly,

these gains were maintained at a three month follow-up, and all patients rated the treatment format as acceptable and that the working alliance with the therapist was high. The authors did note that these results should be interpreted with caution due to the small sample size, lack of a control comparison and blind ratings, and possible selection bias of participants where those who are more comfortable with technologies self-select into the study. However, it was also recognized that the addition of cell phones to the trial allowed for a back-up when teleconferencing equipment did not work, and allowed the clinician to monitor exposure exercises conducted away from the videoconferencing equipment. With the increasing number of cell phones allowing video calls, the potential for this portable technology to improve the capacity for in-situ exposure exercises should only improve with time.

Internet-Based CBT

Treatments that are delivered via computers enable a client to gain assistance from remote locations or from the convenience of their own homes. For some time now, less costly and intense forms of intervention such as bibliotherapy and self-directed exposure have been recognized as an effective option for provision of psychological treatment [33]. More recently, bibliotherapy has been brought into the technological age with the development of computerized versions that as per their original counterparts, do not include any therapist contact. However, on the whole, the evidence has suggested that better results are achieved with the addition of minimal therapist support [34].

A recent open trial of an 8-week CBT treatment ('The OCD Program') delivered via the Internet has been completed [35]. Twenty-two individuals with a primary diagnosis of OCD participated in the trial receiving eight online CBT lessons in addition to twice-weekly telephone contact from a Clinical Psychologist. It should be noted that the average amount of therapist contact time was only 86 minutes across the 8 weeks. Significant improvements in YBOCS total scores were found with a reported within-groups effect size of 1.28 at post-treatment. This suggests that significant improvements in symptoms may be possible with only very limited therapist input.

In another recent open trial [36], 23 patients diagnosed with OCD were provided with a 15-week Internet-Based CBT program with therapist support. Consistent with the Wootton study, therapist contact time was minimal (average of 92 minutes per patient across the entire 15 weeks) and the within-groups effect size on the YBOCS was large (1.56). Taken together, the results of these trials suggest that CBT provided over the Internet with only minimal therapist time can result in substantial symptom reduction of a similar magnitude to that seen in face-to-face studies. However, as these are only open trials randomized controlled trials with larger samples and comparisons against face-to-face CBT are required to strengthen the conclusions.

Virtual Reality

Riva and Gamberini [37] assert that "virtual reality is an application that lets users navigate and interact with a three-dimensional computer-generated environment in real time" (p. 327). Virtual reality can be conducted on a variety of different systems ranging from 3-dimension software installed on a personal computer to immersive headsets connected to a

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hand control [38]. Virtual reality therapies are based on the assumption that people feel "present" in the virtual environment, whereby at some level their perception fails to recognize the role of technology in their experience [39]. A particular advantage of virtual reality systems is that they have the potential to offer accurate standardization and replication of a prescribed environment [40].

Virtual reality therapies have been demonstrated to be more effective than no treatment for several specific phobias, including spider phobia, acrophobia, and a fear of flying [39]. However, head-to-head trials with gold-standard in-vivo ERP treatments are limited, and the value of this form of treatment over the current leading approach is therefore unclear at this stage. The potential cost effectiveness of exposure via a virtual reality system is most obvious for problems where stimuli for the exposure exercise may be difficult or expensive to come by (e.g., flights for exposure exercises to address a fear of flying, or spiders to address a spider phobia). Virtual reality therapies therefore remain a promising area for future directions in anxiety disorder treatment, but require further evaluation at this stage.

In the only study evaluating virtual reality for OCD to date, Clark, Kirkby, Daniels, and Marks [41] used an interactive virtual environment to provide vicarious exposure to dirt for thirteen individuals with OCD. Participants completed three 45-minute computer based treatment sessions at weekly intervals. During the session, the participants were instructed to direct a figure on the screen to engage in exposure, such as by touching dirt in a virtual garden, and encouraged to refrain from selecting that the figure wash their hands in the virtual sink. Participants were awarded points for exposing their figure to dirt, and then for refraining from washing their hands despite the figure rating their anxiety as high. Following treatment, participants showed a significant decrease on their depression scores and on one measure of OCD symptoms, the Padua Inventory. However, no significant change was noted on their YBOCS scores.

In a follow-up report on the same study, it was noted that across the three virtual reality sessions participants became faster at engaging in hand dirtying, and were less likely to engage in hand-washing in the virtual environment [42], indicating that participants were able to learn the principles of ERP via this format. Given the low dose of therapy applied in this trial (i.e., three sessions only), and capacity to provide this treatment without ongoing therapist input, this therapy format certainly warrants further investigation to ascertain whether learning from the virtual environment can generalize to real-world experiences. The main limitation to future development of virtual reality programs for OCD may be the need to create a sufficient range of virtual environments and activities to cater for the expansive variety of OCD symptom presentations beyond contamination fears and associated hand-washing.

Summary of Empirical Evidence for Telemental Health Treatment of OCD

Taken together, the field of telemental health treatment for OCD is very promising with a number of controlled trials now showing that treatments administered via computer with minimal or no therapist assistance can result in significant reductions in obsessive-compulsive symptoms. Particularly promising results are being seen in Internet-Based treatments

whereby as little as ten minutes of telephone contact per week from a therapist is associated with large effect sizes on obsessive-compulsive symptoms. While some approaches may enable reductions in therapist contact hours, approaches such as video-conferencing may not reduce contact hours but instead enable individuals with OCD to receive expert treatment regardless of geographical location. It is therefore envisaged that future treatments within a stepped care model could utilize computer and internet based therapies at a lower step, with technologies such as video-conferencing being used to provide expertise for individuals with high levels of comorbidity or who have not responded to less intense treatment formats who would otherwise have difficulty accessing such services. While the use of virtual reality based programs requires further investigation, it is possible that should it be demonstrated as an effective treatment format, it could be built into current computer or internet based self-help programs as a stand-alone treatment, or as a component in an overall treatment which also includes psychoeducation and the development of a personalized ERP hierarchy.

Metacognitive Therapy

Metacognition refers to beliefs about thinking and strategies used to regulate and control thinking and was originally elaborated upon by Flavell [43]. Since then a number of theorists have incorporated aspects of metacognition into various psychological models of OCD [44-47]. Most notable amongst these theorists is Adrian Wells who, along with colleagues, has developed a comprehensive metacognitive account of OCD based on the Self Regulatory Executive (S-REF) model [48,49]. According to this model, a style of thinking called the cognitive attentional syndrome (CAS) is the main causal factor in prolonging all emotional disorders. However, Wells has gone on to specify which particular aspects of this model are most relevant to understanding OCD. Wells and Mathews [48] and Wells [46] propose that three types of metacognitive knowledge are important in the etiology and maintenance of symptoms: thought fusion beliefs, beliefs about the need to perform rituals, and criteria that signal rituals can be stopped. In this model, thought fusion beliefs are extended beyond thought action fusion (belief that having a thought increases the chance of acting on it) but also thought-event fusion (the belief that having a thought can cause an event or means that an event has happened) and thought object fusion (the belief that thoughts or feelings can be transferred into objects). According to the model the three overall types of metacognitive knowledge operate in a causal chain to explain obsessive-compulsive symptoms.

The main approach used in MCT for OCD is to help the client to become aware of their metacognitive processing and to learn to modify these higher order metacognitions such as beliefs about the importance of thoughts. MCT differs from standard CBT in that no attempts are made to modify lower order appraisals such as 'I am responsible to ensure nothing happens to my family'. Also, MCT does not include exposure exercises aimed at habituation but instead includes the use of behavioural experiments to assist in the interruption of unhelpful metacognitive processes such as attempts to suppress thoughts.

Empirical Evidence for MCT for OCD

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Two small trials of MCT for adults with OCD have been conducted to date. The first case series trial included four individuals diagnosed with OCD who received 12 sessions of individual MCT [50]. Substantial reduction in obsessive-compulsive symptoms was found with all participants meeting clinical significance criteria for recovery at post-treatment and 3-month follow-up. A second open trial included 8 individuals diagnosed with OCD who received 12 sessions of group-based MCT [51]. Similar results were found in this study with seven out of eight participants achieving recovery according to the YBOCS clinical significance criteria. This result was maintained at 3-month follow-up.

Steffen Moritz and colleagues [52] developed and tested a self-help treatment called 'My Metacognitive Training for OCD' (myMCT) which contains a mixture of standard cognitive-behavioural elements plus the addition of metacognitive treatment elements. They recruited 86 individuals with OCD over the Internet and randomly assigned them to either the self-help or wait-list condition. Those in the myMCT condition were emailed an electronic version of the self-help book. Participants who received the intervention showed significantly greater reductions in obsessive-compulsive symptoms compared to the wait-list group. It should be noted that this treatment did contain traditional cognitive restructuring elements and is thus less of a 'pure' test of metacognitive treatment for OCD.

Given that all bar one participant in the earlier MCT trials achieved recovery status and had maintained this at 3-month follow-up, MCT may represent a promising way forward for clinicians and patients alike. As this therapeutic approach does not directly rely on exposure exercises, it may provide a less aversive form of therapy for those who in the past have refused to start or have initiated but then dropped out of ERP programs. The small samples sizes, lack of control conditions, and possible non-specific effects of participating in a group program do limit the conclusions of these trials. Furthermore, there has been no comparison between MCT and gold-standard ERP to date. Further research could go some way towards determining whether MCT fits within the stepped care model of treatment as an efficacious stand alone individual based treatment, an alternative to group ERP or CBT, or as a self-help based program.

Acceptance and Commitment Therapy

ACT is based on a philosophy of *functional contextualism* and the Relational Frame Theory (RFT) [53]. The basic premise of this theory is that individuals learn relationships between stimuli and responses through a number of different processes and this relationship is not necessarily contingent upon actual experience with that stimuli. For example, in the case of OCD a person may fear contamination from handrails because they are similar or grouped together with shopping trolleys which are considered 'dirty'. ACT consists of six main therapy processes that are not targeted in a linear fashion but rather are addressed within therapy when the opportunity or need arises. The six therapy processes are

1. Acceptance,

2. Defusion,

3. Self as context,

4. Contact with the present moment,
5. Values, and
6. Committed Action [54].

Unlike conventional CBT, ACT does not concern itself with attempts to address the content of cognitions or behaviours in OCD but rather the processes. For example, in ACT the client with OCD is assisted to see how previous attempts to control obsessions have failed and that the focus of therapy will shift to 'accept' rather than 'struggle' to eradicate obsessional thoughts. The therapist realigns the client to consider improvement in quality of life as the goal rather than reducing or eliminating symptoms. Another major aspect of the therapy is to help the clients achieve 'cognitive defusion', in other words, to see thoughts less literally. Instead of attempting to analyse, rationally challenge or evaluate the accuracy of thoughts, clients are assisted to 'defuse' from obsessions and to alter their relationship to these experiences by treating them just as thoughts in one's head or 'relatively unimportant words' [55]. Various therapeutic exercises are used to assist the client to achieve defusion such as 'thanking' the mind for a thought. 'Self as context' simply refers to the process of helping the client to separate his or her inner experiences from self. For example, to understand that obsessional thoughts are separate from who the client is as a person. Mindfulness exercises are also used to help the client to become more aware of current experiences, such as thoughts and sensations and not to engage in avoidance but to simply observe and pay attention to those experiences. Values work in ACT focuses on helping the client to follow through on actions or behaviours that are more consistent with personally held values (e.g., being a good friend). This is in contrast to behaviours that are aimed at avoiding anxiety (e.g., completing cleaning rituals). Finally, behavioural commitment exercises are designed to ensure that the client continues to engage in behaviours that are consistent with their values. For example, making time once a week to visit friends would be a behavioural commitment.

Although ACT is described as a Behaviour Therapy and it does include exposure exercises, the difference is that ACT does not utilise these therapeutic strategies with the aim of reducing rituals or distress per se. Rather, all of the strategies are used to help the client practice acceptance and mindfulness whilst heading in valued directions. Often there will be a simultaneous reduction in frequency and distress of obsessions and compulsions as a function of other more functional behaviours taking precedence but this is not the focus of the therapy [55].

Empirical Evidence for ACT with OCD

Twohig, Hayes, and Masuda [56] conducted a multiple baseline study of ACT for OCD that included four clients with different symptom presentations (two checking, one cleaning, one hoarding). The intervention consisted of 8 hours of ACT. At the end of treatment, significant reductions in symptoms were obtained on the Obsessive Compulsive Inventory (OCI) with results maintained at 3-month follow-up. This same ACT protocol was later compared to a progressive relaxation training (PRT) control condition in the first randomized controlled trial of ACT for OCD [57]. The study included 79 adults diagnosed with OCD; with primary symptoms measured using the YBOCS. Significant improvements on the YBOCS were found for the ACT condition at post treatment and follow-up. In addition, clinically signifi-

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cant improvement occurred more in the ACT compared to the PRT condition. Although this study provides initial empirical support for the efficacy of ACT for OCD, further controlled trials are required as well as trials including longer follow-up periods and comparisons against other active and well established treatments such as ERP.

Summary and Conclusion

While ERP has long been established as the most effective treatment for OCD, the typical application of the treatment in an individual face-to-face format may limit client access to effective therapy and specialist clinicians. The stepped-care model suggests that lower intensity treatment formats, such as self-help and group therapy, be utilized so that only those with more complex needs are referred to the higher intensity individual format. This review has indicated that internet based CBT programs with minimal therapist support and group ERP based therapy are supported as lower intensity treatment options within a stepped care model. There is limited evidence that CBT conducted over the telephone or via videoconferencing will reduce therapist time working with patients. These formats therefore do not offer an alternative step within the stepped care model, but instead offer an additional means for delivering the higher intensity step of individual based therapy which is less susceptible to geographical or physical barriers to attending therapy. At this stage, further evaluations are required of virtual reality based programs to ascertain their effectiveness either as a stand-alone treatment or as a component within a treatment package.

Although still considered the gold-standard treatment, some patients will decline to start or complete ERP based therapy, and a proportion will not improve despite application of the treatment by expert clinicians. It is noted that the stepped care model offers limited evidence-based psychological alternatives to ERP based psychotherapy. It is therefore important that we continue to evaluate alternative approaches. Early indications from MCT and ACT trials have shown promising results. However, for both approaches the studies have involved small samples, and neither treatment has been directly compared with ERP in a clinical trial. Until such a comparison takes place, no conclusion can be made as to whether these approaches should be included as an option within the current stepped care model.

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This book collects the contributions of a number of clinical psychiatrists all over the world, interested in developing basic research about anxiety and in applying it in clinical contexts. It is divided into four sections, covering general issues about anxiety (ethological and developmental ones), basic research issues on specific aspects of anxiety (bioanatomical ones, correlation with personality structure and so on), and new clinical and therapeutical proposals and hypothesis. Each author summarized the clinical importance of his work, underlining the clinical pitfalls of this publication.

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