Anxiety and Anguish
Psychological Explorations and Anthropological Figures

Edited by Floriana Irtelli and Fabio Gabrielli

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Meet the editors

Floriana Irtelli is a psychoanalyst, psychotherapist and the International Association for Relational Psychoanalysis and Psychotherapy (IARPP) member who has been lecturing for several years at the Catholic University of the Sacred Heart, Milan, Italy. She has worked at the Fatebenefratelli Hospital, Milan, performing research and clinical activities. She is among the authors of the books *A Fresh Look at Anxiety Disorders* and *Psychopathy - New Updates on an Old Phenomenon*, and has published articles for the *Journal of Affective Disorders*, *Journal Research in Psychotherapy*, and *Journal for Psychiatric and Mental Health Nursing*. She has participated in numerous conferences, seminars, and congresses. She is the sole author of the books *Illuminarsi di Ben-essere*, *Familiar-mente*, and *Contemporary Perspectives on Relational Wellness*.

Professor Fabio Gabrielli (2015 Nobel nominee) is a Full Professor of Philosophical Anthropology at Ludes University of Lugano, Switzerland. He is also a Professor of Philosophy of the Relationship at the School of Management, University Jean Monnet, Bari, Italy. He is also a visiting professor, PWSTE, at the University of Jaroslaw, Poland. Dr. Gabrielli is a member of the International Scientific Committee of the Quantum Paradigms of Psychopathology (QPP) - European section, and a member of the Scientific Board of the Aracne Publishing House in Rome for the Neo-existential Anthropology Series. He is the honorary-national president of CCSVI in Multiple Sclerosis – ONLUS. Dr. Gabrielli has participated in numerous conferences, seminars, and congresses and has authored many books and journal papers.

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Preface

In the present day, numerous studies in the fields of psychology, psychiatry, medicine, anthropology, and sociology are investigating the impact of anxiety and anguish on individuals' mental and physical well-being. This book offers a thorough examination of this subject by delving into research findings, theoretical frameworks, and biopsychosocial viewpoints on anxiety and anguish.

The project has several goals. Firstly, it seeks to provide a detailed analysis of the latest findings from research and clinical studies on the development of anxiety, anguish, and resilience in various modern cultural and anthropological contexts. Secondly, it aims to scrutinize the profound potential of humans and its correlation with mental health. Thirdly, it intends to examine the interplay of demographic factors across diverse psychological and social paths and gather comprehensive data on risk factors contributing to the onset of mental disorders.

Lastly, this book strives to present a summary of risk factors and epidemiological data for the prevention of anxiety and anguish. It ultimately seeks to foster improved life quality, resilience, and psychological wellness in the general populace.

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Section 1

Biology

Chapter 1

Metabotropic Glutamate Receptors in Anxiety Disorder

Jian Xu and Yongling Zhu

Abstract

Anxiety disorders represent a prevalent group of mental health conditions characterized by patients experiencing excessive worry, fear, and distress. The neurobiological underpinnings of anxiety disorders are complex and involve multiple neurotransmitter systems. One such system is the glutamatergic system, which plays a critical role in anxiety regulation. Over the past few decades, much evidence has been gathered, substantiating the involvement of metabotropic glutamate receptors (mGluRs) in anxiety. Consequently, mGluRs have emerged as promising targets for treating anxiety disorders. This book chapter will provide an overview of the role of mGluRs in anxiety, focusing on their involvement in anxiety-related behaviors and their potential as therapeutic targets.

1. Introduction

Anxiety disorders are among the most prevalent mental health conditions worldwide, affecting people of all ages. According to the World Health Organization (WHO), approximately 275 million people suffer from anxiety disorders globally. This staggering number reflects these conditions' profound impact on individuals, families, and communities.

Although the causes of anxiety disorders are not yet fully understood, the condition is believed to arise from a complex interaction of genetic, biological, environmental, and psychological factors [1]. Converging lines of evidence from various branches of neuroscience indicate that anxiety disorders are frequently associated with imbalances in the brain's neurotransmitter systems, including the glutamatergic system [2–7]. Thus, understanding the involvement of the glutamatergic system in anxiety regulation can provide insights into potential therapeutic targets for treatment.

Glutamate is the most abundant excitatory neurotransmitter in the brain. It acts on two primary classes of glutamate receptors, ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). The iGluRs include three subfamilies: N-methyl-D-aspartate receptor (NMDA-Rs),

alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA-Rs), and kainite receptors (KA-Rs). The mGluRs can be classified into group I, group II, and group III [8–10].

Among all glutamate receptors, mGluRs hold particular interest from a pharmacological standpoint for several reasons: (1) Diverse functions: Unlike iGluRs that primarily mediate fast synaptic transmission, mGluRs are involved in a wide range of cellular processes beyond simple neurotransmission. They can influence gene expression, intracellular signaling pathways, and various physiological responses, making them attractive targets for therapeutic intervention. (2) Broader therapeutic scope: Due to their involvement in numerous signaling pathways, targeting mGluRs presents promising opportunities for the development of drugs to address a wide range of conditions and neurological disorders. (3) Modulatory effects: mGluRs modulate synaptic transmission and neural circuitry in more nuanced and complex ways than iGluRs. This modulation allows for fine-tuning of neural activity, which could be beneficial in treating conditions where neural imbalances are involved. (4) Reduced risk of excitotoxicity: iGluRs can mediate excitotoxicity, a process that leads to neuronal damage and death due to excessive glutamate signaling. In contrast, mGluRs do not directly trigger such responses, reducing the risk of harmful side effects. (5) Drug specificity: Targeting mGluRs provides an opportunity to design drugs with better specificity, minimizing off-target effects and increasing therapeutic efficacy. Together, these reasons make mGluRs promising candidates for drug development, offering the potential to treat a wide range of neurological disorders, including anxiety and depression.

The objective of this chapter is to comprehensively examine the roles of mGluRs in anxiety disorders by reviewing the existing evidence. Additionally, we will summarize the findings from preclinical studies investigating the effects of targeting mGluRs for anxiety. Furthermore, this review will also assess results from clinical trials involving mGluR drugs for treating anxiety disorders.

2. Introduction of mGluRs

2.1 History of mGluRs' discovery

In 1985, a groundbreaking discovery occurred when Sladeczek and coworkers demonstrated that glutamate possesses the capability to initiate the formation of molecules associated with a major second messenger system [11]. This finding unveiled the ability of glutamate to stimulate the production of inositol phosphates. Soon after, further evidence for the existence of mGluRs was discovered [12]. Built on these findings, Masu et al. successfully cloned the first mGluR, the mGluR1, in 1991 [13]. Subsequently, seven other mGluR subtypes were cloned by researchers. Together, a total of eight subtypes of mGluRs have been identified in the mammalian system [9]. Over the past three decades, tremendous strides have been made in comprehending the functions of these mGluRs.

2.2 Structure and function of mGluRs

mGluRs are a class of G-protein coupled receptors that bind glutamate. In contrast to iGluRs, mGluRs do not function as ion channels. Instead, their mode of operation

involves initiating complex biochemical cascades. The eight subtypes of mGluRs exhibit distinct characteristics based on their sequence homology, signal transduction mechanisms, and pharmacological properties, leading to the categorization of mGluR subtypes into groups of groups I, II, and III mGluRs [14].

Structurally, all eight mGluRs contain an agonist-binding Venus fly trap (VFT) domain, which uses the cysteine-rich domain (CRDs) to connect to the highly conserved seven-pass trans-membrane domain (7TM) [15]. On cell membranes, mGluRs form obligate dimers. A recent structural study has revealed that when an agonist binds to these receptors' VFT domain, it induces a compaction of the inter-subunit dimer interface. As a result, the CRDs come into close interactions, leading to the repositioning of the 7TM. This conformational change initiates the signaling process [16].

2.3 Insights from mGluR's brain localization

Research on the localization of brain function highlights the association of specific brain regions with distinct functions. For example, anxiety has been linked to specific brain areas, including the hippocampus, prefrontal cortex, amygdala, bed nuclei of the stria terminalis, and hypothalamus [17–19]. Thus, when investigating the involvement of mGluRs in anxiety regulation and development, it becomes essential to examine mGluR's precise expression patterns and localization within these brain regions. In this context, we have compiled mouse brain *in situ* hybridization data from the Allen Brain Institute and present these data in two figures, **Figures 1** and **2**. Please note that immunohistochemistry and in situ, mRNA hybridization have been extensively used to study the expression of mGluRs in the brain, and a wealth of literature is available [9] in addition to Allen Brain Atlas resources. Overall, analysis of mRNA in situ hybridization for different subtypes has led to several crucial observations:

- Diverse expression patterns: The eight mGluRs exhibit distinct expression patterns in the brain, reflecting their varied functions.

- Expression levels: The abundance of mGluRs varies significantly, with mGluR5 and mGluR4 being the most prevalent.

- Anxiety-related brain regions: In line with their role in anxiety regulation, mGluR expression has been identified in various regions, including the hippocampus, prefrontal cortex, amygdala, bed nuclei of the stria terminalis, and hypothalamus. These brain areas are known to be associated with anxiety-related processes.

While the understanding of brain localization of mGluRs in rodents is rather extensive, the localization of mGluRs in humans remains much less explored. However, novel imaging techniques are under active development to investigate the mGluRs in humans. These advancements in imaging studies offer promising avenues to examine the location and abundance of mGluRs in living individuals as well as in postmortem tissue [20–22]. Undoubtedly, future human studies will provide valuable insights into the brain localization of mGluRs, deepening our understanding of their potential roles in anxiety.

Figure 1.
In situ hybridization of mGluR1–8 in mouse brain sagittal slices. Images were exported from Allen brain institute (https://mouse.brain-map.org/). At the bottom is the brain atlas with arrows pointing to hippocampus and amygdala. The sagittal plane is about 3.0 mm from the midline. Scale Bar, 1200 µm.

Figure 2.
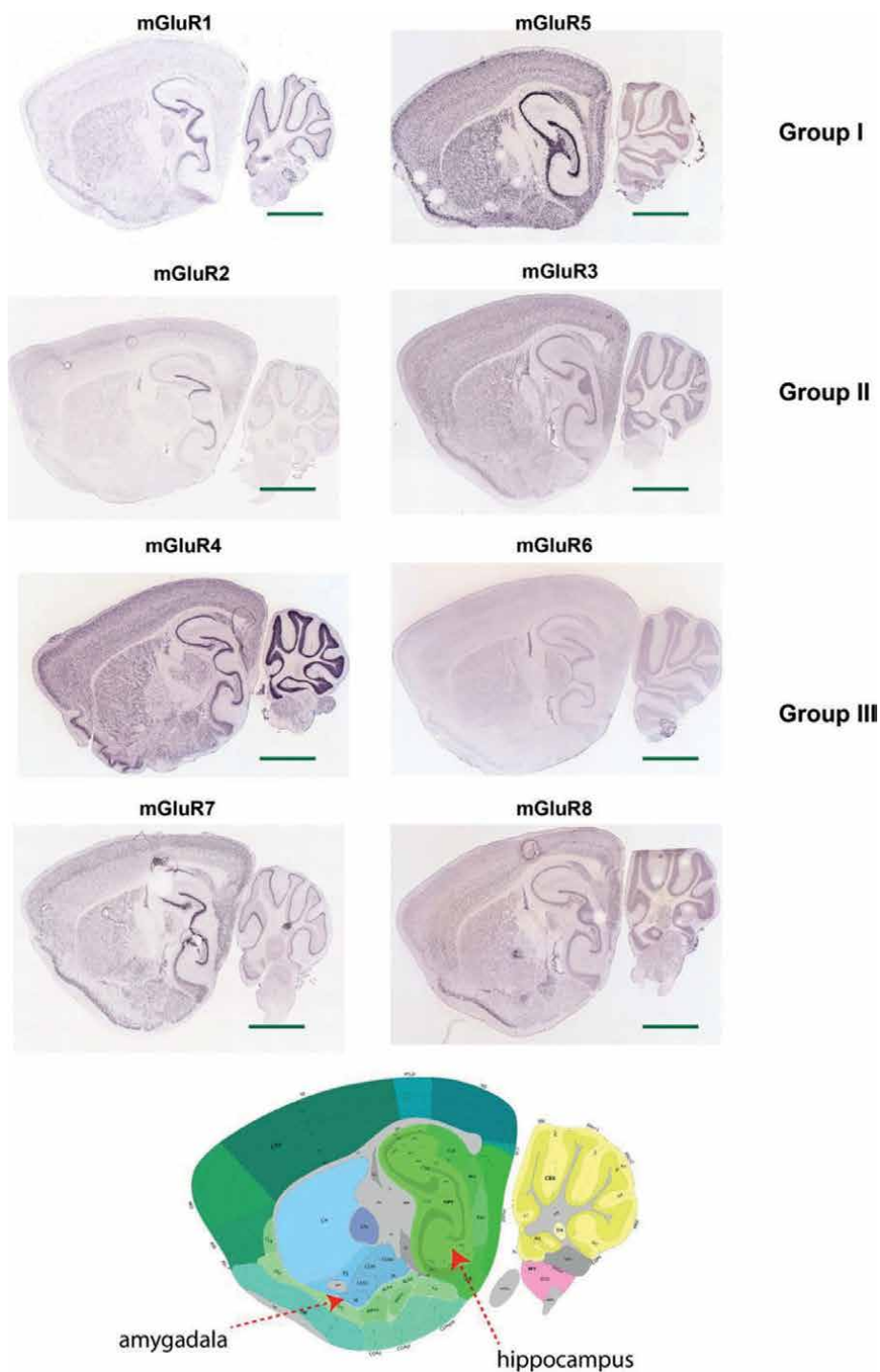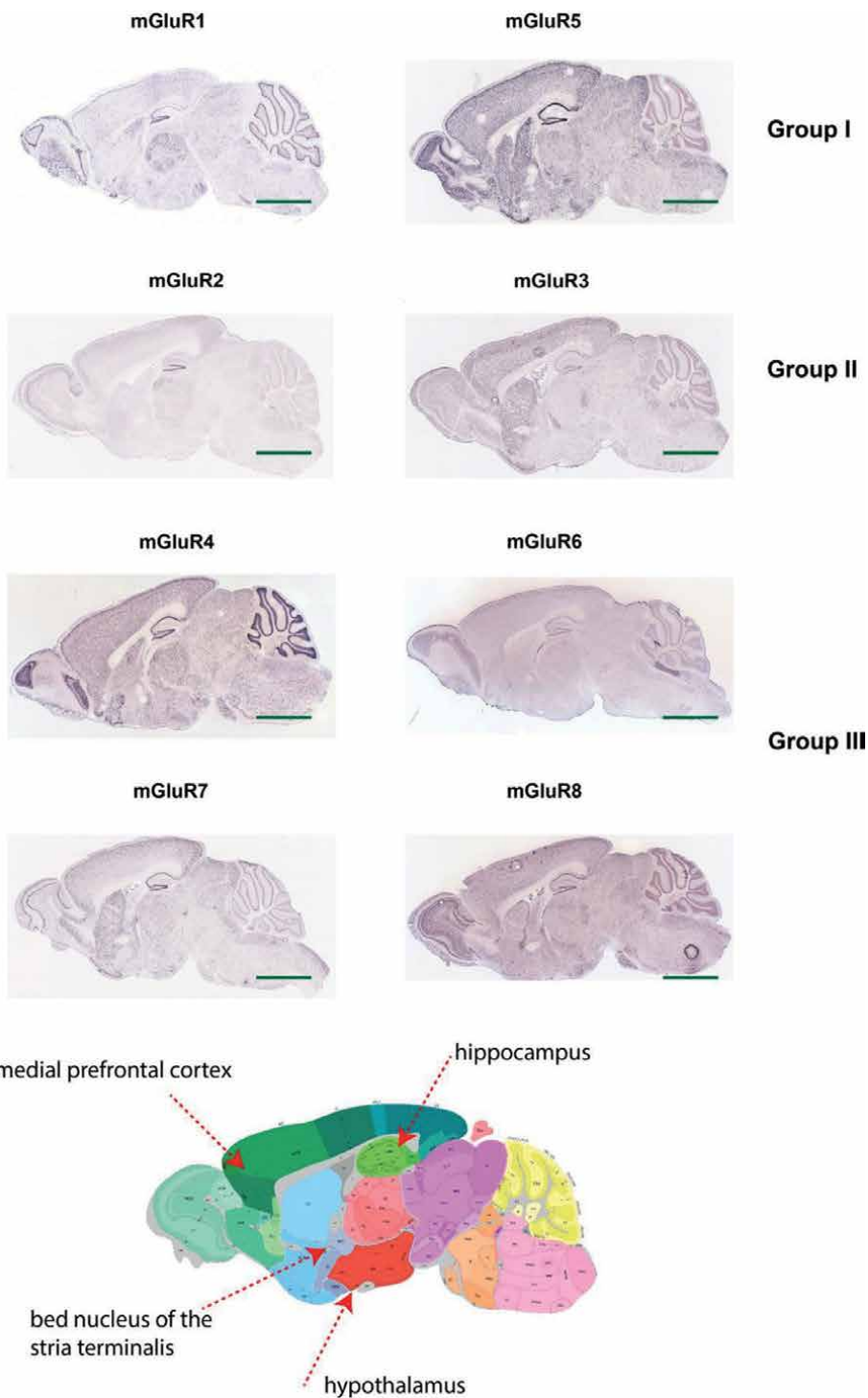*In situ hybridization of mGluR1–8 in mouse brain sagittal slices. Images were exported from Allen brain institute (https://mouse.brain-map.org/). At the bottom is the brain atlas with arrows pointing to hippocampus, hypothalamus, bed nucleus of the stria terminalis (BNST) and medial prefrontal cortex, and amygdala. The sagittal plane is about 0.5 mm from the midline. Scale Bar, 1200 μm.*

2.4 Subtypes of mGluRs

2.4.1 Group I mGluRs

Group I mGluRs consist of two subtypes: mGluR1 and mGluR5. Both mGluR5 and mGluR1 receptors are primarily located postsynaptically in the central nervous system (CNS). They play important roles in regulating synaptic transmission, neuronal excitability, and plasticity [9, 23–26].

mGluR1 and mGluR5 display structural similarities and share common signaling mechanisms. Upon binding with glutamate, they both initiate the activation of the Gq/11 protein, subsequently leading to the activation of phospholipase C (PLC). PLC hydrolyzes phosphatidylinositol bisphosphate (PIP2) into inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 then promotes the release of calcium ions from intracellular stores, while DAG activates protein kinase C (PKC). These intracellular signaling pathways mediate the effects of group I mGluRs.

In the brain group I mGluRs are predominantly expressed in the hippocampus, cortex, and striatum, where they modulate synaptic transmission and synaptic plasticity. These receptors involve in many physiological processes, including motor activities, learning and memory, neuronal development, addiction, and emotion regulations [26–32]. Clinically, group I mGluRs have been associated with various neurological conditions, encompassing anxiety, depression, epilepsy, Parkinson's disease, and fragile X syndrome. Consequently, these receptors have become potential targets for therapeutic interventions [33–36].

2.4.2 Group II mGluRs

Group II mGluRs have two subtypes: mGluR2 and mGluR3 [37]. They are primarily located presynaptically in CNS where they act as autoreceptors [38]. Activation of mGluR2 or mGluR3 predominantly elicits an inhibitory response through a G-protein-coupled mechanism. When glutamate binds to group II mGluRs, it triggers the activation of G i/o proteins. The activated G i/o proteins inhibit adenylate cyclase (AC), leading to a decrease in cyclic AMP (cAMP) levels. The reduction in cAMP ultimately results in the inhibition of neurotransmitter release. Additionally, the dissociated beta-gamma subunits of the G-protein may modulate the activity of ion channels, leading to changes in membrane potential and ion flow across the cell membrane [39].

mGluR3 exhibits broad expression in CNS, whereas mGluR2 displays limited and overall low expression. It shows modest expression in the dentate gyrus and olfactory regions and weak expression in the thalamus, striatum, and cortex.

The functions of group II mGluRs have been associated with various physiological functions such as motor activities, learning and memory, emotion regulation, addiction, and neuroprotection [40–45]. Group II mGluRs are also implicated in pathological conditions such as anxiety, depression, schizophrenia, pain, and neurodegenerative disorders [33, 46, 47].

2.4.3 Group III mGluRs

Group III mGluRs include four subtypes: mGluR4, mGluR6, mGluR7, and mGluR8. They are coupled to heteromeric Gi/Go protein. Activation of group III mGluRs also leads to the inhibition of adenylate cyclase [9].

Among the four group III mGluRs, mGluR6 is primarily located in the ON-bipolar cells of the retina [48]. In contrast, mGluR4, mGluR6, and mGluR7 are expressed in CNS with relatively widespread distributions. Specifically, mGluR4 is found in most brain regions, displaying the highest intensity in the cerebellum and moderate levels in the cortex, striatum, amygdala, and hippocampus. On the other hand, mGluR7 exhibits high expression in the hippocampus, and it also demonstrates a relatively strong presence in the amygdala and striatum. Although mGluR8 was initially identified in the retina [49], it is also expressed in the CNS, particularly in regions like the cerebellum, olfactory bulb, cortex, and hippocampus. However, the expression levels of mGluR8 in these CNS regions are lower than that of mGluR4.

Like group II mGluRs, group III mGluRs are also primarily located in the presynaptic terminals of neurons in the CNS [50], where they act as autoreceptors, responding to the release of glutamate from the same neuron to regulate neurotransmitter release. Group III mGluRs can also be found on postsynaptic neurons, which modulate postsynaptic responses to neurotransmitter signaling [51].

mGluR4 and mGluR8 have a much higher affinity to glutamate than mGluR7, which shows a low affinity for glutamate and is activated only by high glutamate concentrations [52, 53]. Overall, these versatile receptors play crucial roles in a wide range of physiological processes, including motor functions, learning and memory, fear extinction, anxiety, social behaviors, and epilepsy [54–60]. Furthermore, their implications extend to human neurological conditions, including epilepsy, anxiety disorders, depression, pain modulation, and addiction [33, 61, 62].

3. Preclinical studies for the roles of mGluRs in anxiety

3.1 History

Shortly after discovering mGluR genes in the 1990s, researchers began exploring the functions of mGluR subtypes at glutamatergic synapses and the possible roles of mGluRs in neurological disorders, including anxiety. Numerous preclinical studies have been conducted to examine the effects of different mGluR compounds in animal models of anxiety. Encouragingly, a considerable body of evidence has quickly emerged and confirmed that some mGluR compounds demonstrate anxiolytic and antidepressant-like properties in animal models. Particularly, studies in rodents have shown that antagonists of group I mGluRs, and agonists of group II mGluRs can act as anxiolytics and antidepressants [63–69]. These findings have laid a solid foundation for further research in this promising field.

Besides the pharmacological approach, mGluR mutant animal models have also been developed and tested extensively to explore mGluRs' role in anxiety. Furthermore, through electrophysiological, cellular, and biochemical studies, optogenetics and chemogenetics, valuable insights have been gained into the specific modulation of synaptic transmission, intrinsic excitability, and synaptic plasticity of mGluRs in brain regions that govern emotions and anxiety, such as the amygdala, hippocampus, and prefrontal cortex [19, 70, 71].

Together, these collective data from preclinical research have significantly deepened our understanding of anxiety disorders' molecular and neural foundations. Furthermore, these studies offer promising therapeutic avenues by targeting mGluRs for potential anxiety treatments.

3.2 Roles of group I mGluRs in anxiety

Group I mGluRs have long been implicated in regulating anxiety and anxiety disorders. These receptors are primarily expressed in brain regions associated with emotional processing, including the amygdala, prefrontal cortex, and hippocampus.

Numerous animal studies investigating drugs targeting group I mGluRs and their effects on anxiety-like behaviors have been conducted, yielding consistent findings. Overall, antagonistic treatment has shown significant anxiolytic responses in experimental animals, indicating their potential as therapeutic agents for anxiety-related disorders. These compounds have demonstrated a notable capacity to lower anxiety levels in preclinical models. This is supported by their ability to reduce fear-conditioned freezing, increase the time spent in the center of the open field, and decrease marble-burying behavior, among other positive indicators. However, it is important to point out that the anxiolytic effects of group I mGluR compounds may vary based on their specific brain region activation. Activation of mGluR1 or mGluR5 in particular brain regions, such as the hippocampus, amygdala, and the prefrontal cortex, may be particularly relevant to anxiety regulation. Also, the effects of group I mGluR compounds on anxiety may exhibit dose-dependent responses, with different outcomes observed at varying concentrations.

Owing to their significance and relevance, a plethora of exclusive reviews are available on animal studies focusing on drugs targeting group I mGluRs. Consequently, readers can refer to these articles to delve into comprehensive details regarding drug studies. Here are a few illustrative examples. Swanson et al. reviewed in 2005 animal studies on drugs targeting mGluRs on anxiety-like behaviors [72]. Krystal et al. reviewed in 2010 the preclinical animal studies that examined mGluR agonists and antagonists in rodent models of anxiety [73]. Of the studies examined in this 2010 review, about 90% of them reported an anxiolytic effect with mGluR5 antagonists. Riaza Bermudo-Soriano et al. provided another review [3]. In this comprehensive review conducted in 2012, the authors examined the effects of mGluR5 antagonists on anxiety through 43 animal studies. Remarkably, all but two of these studies revealed anxiolytic effects, indicating a strong potential for mGluR5 antagonists in anxiety treatment. Additionally, the authors assessed 20 animal studies involving mGluR1 antagonists and their impact on anxiety. Among these studies, an encouraging 13 of them demonstrated anxiolytic effects, further highlighting the promising therapeutic role of mGluR1 antagonists in addressing anxiety-related conditions.

3.3 Roles of group II mGluRs in anxiety

mGluR3 exhibits broad expression in many brain regions, including those known to be involved in emotional processing, such as the amygdala, prefrontal cortex, hippocampus, and bed nucleus of the stria terminalis. In contrast, mGluR2 shows a more limited expression pattern, with moderately strong presence in the dentate gyrus and olfactory regions and weaker expression in the thalamus, striatum, and cortex.

Group II mGluRs inhibit the release of glutamate, and by reducing excessive glutamate release, these receptors can help regulate neuronal activity and maintain a balance in the brain's excitatory signaling, which may contribute to anxiety reduction. Indeed, many animal studies on drugs targeting the group II mGluRs on anxiety-like behaviors have been conducted, and rather consistent findings have been reported.

Overall, agonists and positive allosteric modulators of mGluR2 and/or mGluR3 receptors have been found to elicit anxiolytic responses in experimental animals. For example, mGluR2/3 agonists have been shown to reduce fear-potentiated startle, decrease stress-induced hyperthermia, and increase open-arm entries in the elevated plus maze [43, 74, 75]. Other studies showed that pharmacological activation of mGlu2/3 receptors shortens the time that was required for the conventional antidepressants to be effective as antidepressants in these rats, proposing the combination of mGluR2/3 agonists with other antianxiety agents as a potential treatment for anxiety [76, 77]. In line with the preclinical antipsychotic pharmacology of the mGlu2/3 receptor agonist, Nasca et al. showed that L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors [78].

While it was somewhat expected that mGluR2/3 agonists might act as antianxiety agents, as mentioned earlier, some later studies brought about surprising findings. These studies revealed that negative allosteric modulators targeting mGluR2/3 also exhibited antidepressant and anxiolytic activity in rodents. The anxiolytic effect was demonstrated in various behavioral paradigms, including the learned helplessness (LH) paradigm [79], marble-burying, and forced swim test (FST) [80]. Therefore, these results suggest that the blockade mGluR2/3 may also hold promise as a treatment for depressive and anxiety disorders. In the 2012 review by Riaza Bermudo-Soriano et al., nine studies with mGluR2/3 antagonists were listed, with six demonstrated anxiolytic effects. Meanwhile, 28 studies with mGluR2/3 agonists were recorded, all but three demonstrated anxiolytic effects [3].

As such, the anxiolytic effects observed with the blockade or activation of mGluR2/3 have led to some conflicting findings. While the exact reasons for these discrepancies remain not fully understood, various factors, such as differences in behavioral assays, routes of drug administration, and dosages, may play a significant role in the observed outcomes. Therefore, it is imperative to conduct further research and engage in in-depth discussions to fully elucidate the potential of mGluR2/3 agonists or antagonists in anxiety treatment.

3.4 Roles of group III mGluRs in anxiety

The expression patterns of group III mGluRs indicate that they might also play significant roles in anxiety regulation. Notably, mGluR4, mGluR7, and mGluR8 are all present in the hippocampus, and there is a possibility of mGluR6 having low expression in this region as well. Additionally, these receptors, mGluR4, mGluR7, and mGluR8, are found in other crucial areas such as the hypothalamus, prefrontal cortex, and amygdala. Given their presence in these regions, the activation of these receptors could potentially influence synaptic transmission and impact anxiety-related processes.

While the specific roles of each subtype of group III mGluRs in anxiety are still an active area of research, evidence also suggests their involvement in anxiety regulation. Group III mGluR ligands have been comparatively less studied for their efficacy in anxiety disorders when compared to group I and II ligands; nevertheless, a substantial number of studies have been conducted thus far. Notably, the administration of group III mGluR agonists has demonstrated anxiolytic-like and antidepressant-like effects in experimental animal models. For example, Systemic administration of mGluR8 receptor agonist (S)-3,4-DCPG induces c-fos in stress-related brain regions in wild-type but not mGluR8 receptor knockout mice, suggesting that mGluR8 receptors are involved in anxiety regulation [81]. Several studies have demonstrated

that the administration of group III mGluR agonists results in anxiolytic-like and antidepressant-like effects in behavioral tests [82–84]. In a separate study, mGluR4 PAM exhibited an anxiolytic effect but did not produce an antidepressant-like effect [85]. Recently, mGluR7 specific agonist was also found to be able to produce anxiolytic effects [86]. Compared to mGluR4, mGluR7, and mGluR8, the role of mGluR6 in anxiety remains uncertain. This uncertainty arises from its predominantly expressed location in the retina, with very low expression in the CNS. However, when tested in rats, pharmacological activation of mGluR6 in vivo using a selective agonist produced some anxiolytic-like effects, suggesting mGluR6 might also play a role in anxiety-related processes [82].

In summary, research indicates that among the four group III mGluRs, mGluR4, mGluR7, and mGluR8 are all associated with anxiety behaviors. Additionally, mGluR6 might also play a role in anxiety, though its involvement requires further investigation. Despite the progress over the years, the specific roles of the group III mGluR subtypes in anxiety remain largely unknown, emphasizing the need for further research to elucidate their exact functions and significance in anxiety behaviors.

3.5 mGluR animal models in anxiety

Alongside the pharmacological approach, researchers have extensively developed and tested mGluR mutant animal models to explore the roles of these receptors in anxiety. Constitutive knockouts for all mGluR genes have been generated [26, 42, 45, 56, 59, 87–89], and conditional knockout mice for specific mGluR genes have also been created [28, 34, 90]. Using mutant animals provides a significant advantage in terms of subtype precision, allowing researchers to target specific mGluR subtypes, which can be challenging to achieve with pharmacological compounds. However, it is crucial to acknowledge the limitations of knockout studies using mutant animals, such as potential gene compensation issues. Despite these challenges, using mutant animal models remains a valuable tool in advancing our understanding of mGluRs' involvement in anxiety and related processes. **Table 1** presents the findings from studies involving mGluR mutant mice.

As summarized above, *Grm1* ko mice exhibit significant impairments in movement and gait [87], which pose challenges in interpreting behavioral measurements. Despite that, the *Grm1* ko mice displayed a significant prepulse inhibition (PPI) deficit [32]. It is noteworthy that reduced PPI has been observed in patients with certain anxiety disorders [97, 98]. On the other hand, there is some disagreement in the effects of *Grm5* ko mice when compared to the impact of mGluR5 agonists. Considering the consistent and robust anxiolytic effects of mGluR5 antagonists, it was expected for the *Grm5* ko mice to display reduced anxiety. Indeed, in the open field test (OFT) and Marble-Burying Test (MBT), the *Grm5* ko mice showed less anxiety. However, *Grm5* ko mice also exhibited severe impairments in fear extinction [28], widely considered a key mechanism in posttraumatic stress disorder (PTSD). This finding suggests that an agonist of mGluR5, instead of an antagonist, may be helpful as a treatment option to treat severe anxiety in people who have experienced traumatic events [99, 100].

Despite the clear anxiolytic effects observed in mGlu2/3 ligands, the lack of an anxiety phenotype in *Grm2* ko and *Grm3* ko mice, as well as the double ko mice, was unexpected. But the anxiolytic-like activity of LY354740 in wild-type mice was not evident in either *Grm2* or *Grm3* ko mice, suggesting that anxiolytic-like activity was indeed meditated by mGluR2 and mGluR3 [43]. The exact reason for the unaltered

Gene	Model	Test	Behavior phenotypes	Anxiety	Ref
Grm5	ko	OFT	*Grm5* ko mice spent more time in the middle of the arena compared to the control.	⇓	[27, 91, 92]
Grm5	ko	MBT	Marble burying is abolished in *Grm5* ko mice.	⇓	[27]
Grm5	ko	EZM	No change in the time animals spent exploring the open area in *Grm5* ko mice.	⇔	[27]
Grm5	ko	FE	Fear extinction is impaired in *Grm5* ko mice.	⇑	[28]
Grm5	ko	EZM, DLB	*Grm5* ko mice showed increased anxiety accentuating with aging.	⇑	[93]
Grm1	ko	PPI	*Grm1* ko mice exhibited a significant PPI deficit despite their smaller body size and abnormal gait. Note: Evidence exists for the coupling of reduced PPI and certain anxiety disorders.	⇑	[32]
Grm2	ko	EPM, OFT, BWA	no consistent effect on anxiety in *Grm2* ko mice.	⇔	[94]
Grm3	ko	EPM, OFT BWA	no consistent effect on anxiety *Grm3* ko mice.	⇔	[94]
Grm3 and *Grm2*	double ko	EPM, OFT BWA	No consistent effect on anxiety in *Grm2/Grm3* double ko mice.	⇔	[94]
Grm2	ko		*Grm2* ko and *Grm3 ko* mice were grossly normal. However, the anxiolytic-like activity of LY354740 (20 mg/kg, s.c.) was not evident in either *Grm2* or *Grm3* ko mice.	⇔	[43]
Grm3	ko	DLB, EPM, OFT	No difference on anxiety	⇔	[40]
Grm4	ko	OFT, EZM	middle-aged *Grm4* ko male mice showed increased measures of anxiety in the open field and elevated zero maze.	⇑	[95]
Grm4	ko	OFT, EZM	No changes in adult 6-month-old *Grm4* male ko mice.	⇔	[95]
Grm4	ko	OFT, EZM	female *Grm4* ko mice showed reduced measures of anxiety.	⇓	[95]
Grm6	ko	not available			[88]
Grm7	ko	OFT	*Grm7* ko mice spent significantly more time exploring the open arms of the maze.	⇓	[60]
Grm7	ko	LDB, EPM, staircase test, SIH	*Grm7* ko mice displayed anxiolytic activity in four different behavioral tests, i.e., the light-dark box, the elevated plus maze, the staircase test, and the stress-induced hyperthermia test,	⇓	[96]

Gene	Model	Test	Behavior phenotypes	Anxiety	Ref
Grm8	ko	OF,EPM	*Grm8* ko mice showed increased measures of anxiety in the open field and the elevated plus maze, and an increased acoustic startle response were seen in 6- and 12-month-old *Grm8* ko male mice.	⇑	[58]

Abbreviations: OFT: open field test, EZM: Elevated zero maze, DLB: Dark–Light Box test, FPS: Fear-potentiated startle, VC: Vogel conflict test, BWA: The Black & White Alley, SIH: stress-induced hyperthermia test.
Note: in mice, mGluR1–8 are encoded by Grm1–8 genes respectively.

Table 1.
Anxiety-related behaviors in Grm1–8 ko mice.

anxiety in these knockout mice remains unknown. One possible explanation could be the presence of redundancy and compensation mechanisms. However, even in the *Grm2/Grm3* double ko mice, the anxiety-like behaviors were not significantly affected, which suggests that redundancy and compensation alone may not fully account for the observation. Another plausible explanation could be that *Grm2* and *Grm3* ko mice may experience developmental changes, which could influence the outcome. Future testing with conditional knockout mice may prove helpful to further investigate and resolve this discrepancy.

The behavioral effects of knocking out genes for group III mGluRs, *Grm4*, *Grm6*, *Grm7*, and *Grm8*, were also quite intricate. In the case of *Grm4* ko mice, the consequences of gene deletion were discovered to be dependent on age and gender [95]. Interestingly, *Grm7* ko mice exhibited reduced anxiety [60, 96], while *Grm8* ko mice displayed increased anxiety [58]. These outcomes do not entirely align with the pharmacological results, where the administration of group III mGluR agonists generally produces anxiolytic effects. As a result, further studies are necessary to address and clarify these discrepancies.

4. Human studies linking mGluRs in anxiety disorders

4.1 History

In 1982, a clinical study was published demonstrating the potential efficacy of fenobam in treating anxiety [101]. At that time, the specific target of fenobam was not yet known, and it was not until 20 years later that Porter et al. [102] discovered that fenobam actually acted as a selective and potent mGluR5 receptor antagonist. As a result, the 1982 study [101] provided the initial evidence for the involvement of mGluRs in anxiety, marking an essential milestone in comprehending the roles of these receptors in anxiety disorders. Since the 1982 report, numerous additional studies have been conducted, encompassing both animal studies and preclinical and clinical investigations. Collectively, these studies have overwhelmingly supported the roles of mGluRs in anxiety. The expanding body of evidence reinforce the initial findings and solidify our understanding of mGluR's importance in anxiety disorders [33, 35, 73, 103, 104].

It is worth noting that mGluRs have been implicated in obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD), both of which were

previously classified as anxiety disorders before the introduction of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Additionally, while this chapter focuses on mGluR in anxiety disorder, it is important to highlight that mGluRs are also implicated in depression disorders. Although anxiety and depression are distinct disorders with unique characteristics, they often co-occur and share some similarities in symptoms and treatment approaches. Many individuals experience symptoms of both conditions simultaneously, leading to what is known as comorbid anxiety and depression. Therefore, this section also includes specific clinical evidence that implicates mGluRs in depression.

4.2 Findings from human genetic studies

Genetic linkage and association studies have been extensively conducted to identify chromosomal risk loci and susceptibility genes for anxiety and depression [105]. Among the findings, there is a multiple of evidence supporting the roles of *GRM* genes in anxiety (see **Table 2** for details). Particularly, at least four studies have implicated either GRM7 or GRM8 in depression disorder [106–109], giving strong support for the involvement of group III mGluRs in depression. Furthermore, genetic studies have strongly indicated the involvement of GRM5 in autism spectrum disorder (ASD) [110–113]. Although ASD and anxiety are distinct conditions, it is worth noting that many ASD patients also experience anxiety disorder. As a result, these human genetic studies may offer insights into potential shared neural mechanisms underlying depression, anxiety, and even ASD, despite their different diagnostic classification.

	Studies	Findings	Reference
GRM7	Linkage studies	There is a genome-wide significant linkage to chromosome 3p26-3p25, with a peak signal near the gene *GRM7* in depression.	[106, 107]
GRM8	GSAA	The glutamatergic synaptic transmission gene set (GO:0035249) includes 16 genes, of which six genes, *SLC1A4*, *CACNA1A*, *GRM8*, *PARK2*, *UNC13A*, and *SHC3*, showed nominal association with MDD.	[108]
GRM8	GWAS	A plausible biological association was found with SNPs within *GRM8* in depression.	[109]
GRM5	WES, GWAS	High throughput sequencing has identified *de novo GRM5* mutations and enrichment of rare variants of genes encoding components of mGluR signaling pathways. Increase in the prevalence *GRM5* copy number variants in ASD was reported.	[110–113]

Abbreviations: GSAA: gene-set-based association analysis, GWAS: genome-wide association scans, WES: whole-exome sequencing, ASD: autism spectrum disorder, MDD: major depression disorder, SNPs: single nucleotide polymorphisms.

Table 2.
Evidence from genetic studies implicating GRM genes in anxiety.

4.3 Findings from emission tomography (PET)

PET has emerged as a valuable tool in diverse neurologic and psychiatric applications. Particularly, over the last two decades, significant advancements have been made in developing mGluR PET ligands, leading to an increasing number of PET radioligands that target mGluRs. These innovative ligands provide a noninvasive in vivo imaging technique, enabling the quantification of mGluR receptors in normal and disease-state conditions [7, 114].

For group I mGluRs, the pioneer tracer for both preclinical and clinical applications, [11C]ABP688, was developed in 2006 [115]. Since then, several more radioligands have been introduced, including [18F]FIMX for mGluR1 [116], [18F]FPEB [117], and [18F]SP203 [118] for mGluR5. These radioligands have been employed in clinical trials and have played a pivotal role in investigating the involvement of mGluRs in anxiety disorders. Among these ligands, mGluR5 has been the most extensively studied. The critical findings for these studies are summarized in **Table 3**. Interestingly, it appears that mGluR5 expression can vary significantly, showing

Receptors	Ligands	Disorders	Findings	mGluR5	Ref
mGluR5	[^{18}F]FPEB	MDD	No significant between-group differences were observed. Individuals with MDD had higher ACC glutamate, Importantly, the ACC mGluR5 DVR negatively correlated with glutamate.	⇔	[22]
mGluR5	[^{11}C]ABP688	MDD	mGluR5 density reduced in the amygdala and prefrontal cortex in MDD.	⇓	[21]
mGluR5	[^{18}F]FPEB	PTSD	There is significantly higher mGluR5 availability in individuals with PTSD relative to matched controls across many brain regions.	⇑	[119]
mGluR5	[^{18}F]FPEB	Suicidal ideation	There is higher availability of mGluR5 in individuals with PTSD than healthy control and MDD groups. Furthermore, higher mGluR5 availability was associated with scan-day suicidal ideation among individuals with PTSD, but not MDD.	⇑	[120]
mGluR5	[11C]ABP688	OCD	There is higher mGluR5 availability in OCD patients.	⇑	[121]
mGluR5	[^{11}C]ABP688	MDD	No significant difference in mGluR5 availability was observed between elderly subjects with MDD and healthy volunteers.	⇔	[122]

Abbreviations: MDD: major depressive disorder, PTSD: posttraumatic stress disorder, OCD: obsessive-compulsive disorder, ACC: anterior cingulate, DVR: distribution volume ratio.

Table 3.
Imaging studies of mGluRs in human.

either upregulation or downregulation depending on the specific disorder. For instance, individuals with MDD may exhibit lower levels of mGluR5, while those with PTSD may experience upregulation of this receptor (**Table 3**). As a result, when contemplating pharmacological interventions targeting mGluRs, it becomes crucial to meticulously justify their usage based on how the receptors are altered in different medical conditions.

As of now, some PET ligands have also been developed for group II mGluRs, specifically targeting mGluR2 and mGluR3, with [11C]JNJ42491293 [123] being a notable ligand that has been used in clinical studies to probe mGluR2 in the human brain. On the other hand, the availability of group III PET ligands remains limited [124]. Although several ligands have been developed for PET imaging purposes, there is currently a lack of reports on their usage in human patients.

5. Clinical studies

The utilization of pharmacological modulation of glutamate transmission has long been regarded as a highly valuable therapeutic approach [3, 125, 126]. The mGluRs have emerged as potential targets for safely altering glutamate-driven excitation. Preclinical data support the potential therapeutic use of mGluR modulators in the treatment of anxiety, depression, schizophrenia, and other psychiatric disorders, pain, epilepsy, as well as neurodegenerative and neurodevelopmental disorders [3, 72, 73, 127]. Numerous clinical trials have been conducted to explore the potential of targeting mGluRs for treating various neurological diseases. A recent review comprehensively summarized the findings from these clinical studies involving compounds that specifically interact with mGluRs [104].

Anxiety disorders are the most common mental disorders, affecting about 30% of the population at some point in life. Given the involvement of mGluRs in anxiety regulation, there has been tremendous interest in developing mGluR drugs for therapeutic use in anxiety disorders. Indeed, a number of mGluR antagonists or agonists have been used in clinical studies of anxiety disorder. These data are summarized in **Table 4**.

Currently, the only FDA-approved medication targeting mGluRs is fenobam, which initially received approval as an anxiolytic [101] before its characterization as a mGluR5 receptor antagonist [102]. Despite numerous clinical trials exploring mGluR-targeting compounds for treating anxiety, OCD, depression, and panic disorder, the results have not been as promising as anticipated. Notably, three studies targeting group II mGluRs [130–132] and two studies targeting mGluR5 [128, 129] did not yield the robust outcomes desired. The development of group III mGluRs as potential therapeutic targets has been relatively limited compared to other mGluR receptors. As of now, there have been no reports of human clinical trials involving group III compounds.

Rest assured, laboratories' dedication to developing novel mGluR drugs will persist, and preclinical research will continue to advance our understanding of mGluR functions. Despite encountering various challenges, clinical inquiry into mGluRs will not cease. There remains a hopeful outlook that effective treatments can be developed based on the functions of mGluRs. With ongoing efforts and scientific exploration, we can aspire to find new therapeutic approaches for anxiety disorders.

Compounds	Receptor	Study	Findings	Reference
Fenobam	mGluR5 antagonist	Anxiety disorder	Approved by FDA for anxiety treatment.	[101]
Basimglurant	mGluR5 antagonist	MDD	The primary endpoint (mean change in clinician-rated MADRS score from baseline to end of treatment) was not met.	[128]
Mavoglurant	mGluR5 antagonist	OCD patients that are unresponsive to SSRI therapy	This study of mavoglurant in OCD was terminated because of the lack of efficacy in the interim analysis.	[129]
LY354740	mGlu2/3 agonist	Panic disorder	LY354740 failed to show treatment effects that were different from placebo.	[130]
LY544344	mGlu2/3 agonists	Phase 2 GAD	Improvements in HA and CGI. However, the trial was discontinued early based on findings of convulsions in preclinical studies.	[131]
JNJ-40411813	mGlu2 agonist	Phase 2a study in MDD patients with significant anxiety symptoms	No efficacy signal was detected on the primary endpoint, the 6-item Hamilton Anxiety Subscale.	[132]
Pomaglumetad methionil	mGlu2/3 agonist	PTSD Fear-potentiated startle	Result not disclosed.	ClinicalTrials.gov Identifier: NCT02234687
Decoglurant	mGlu2/3 antagonist	Major depressive disorder patients taking SSRI or SNRI antidepressants	No significant separation from placebo on depression or cognition endpoints (high placebo response rate).	[133]

Abbreviations: HA and CGI: Hamilton Anxiety and Clinical Global Impression, MDD: major depressive disorder, OCD: obsessive-compulsive disorder, GAD: generalized anxiety disorder, HDR: Hamilton Depression Rating, MADRS: Montgomery-Asberg Depression Rating Scale, SSRI: selective serotonin reuptake inhibitors, SNRIs: serotonin and norepinephrine reuptake Inhibitors.

Table 4.
Clinical studies on the effects of mGluR compounds on anxiety disorders and related conditions.

6. Conclusion

This book chapter offers a comprehensive investigation into the roles of mGluRs in anxiety disorders. Through an exploration of their classification, neurobiological mechanisms, and potential therapeutic implications, the aim is to enhance our understanding of these receptors as potential targets for developing innovative treatments for anxiety disorders. The chapter begins with an exploration of the biology of mGluRs. It then transitions to an investigation of how mGluRs influence

anxiety-related behaviors in animals, utilizing animal models as a foundation to understand the neurobiological mechanisms underlying the actions of mGluRs. In the subsequent section, the chapter delves into the clinical implications and therapeutic potential of mGluRs in anxiety disorders.

Preclinical data strongly supports the potential of mGluRs as promising therapeutic targets for anxiety disorders. A wealth of evidence demonstrates that certain mGluR compounds exhibit high efficacy as anxiolytic agents in animal models. However, from a mechanistic standpoint, many important questions remain unanswered, such as the specific roles of individual receptors and the underlying cellular mechanisms and neural circuits through which these receptors ultimately influence anxiety. Further research is needed to address these aspects and fully harness the therapeutic benefits of targeting mGluRs for anxiety disorders.
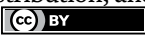
Unfortunately, despite initial expectations, the clinical studies on mGluR receptor ligands as anxiolytics have yielded somewhat disappointing results. However, we should approach this situation with cautious optimism. It is crucial to recognize that these ligands have been tested only in a limited range of anxiety disorders, and their full therapeutic potential remains yet to be defined. There is hope that through further exploration and broader clinical trials, more promising outcomes for these ligands may be revealed. Furthermore, ongoing advancements in developing new compounds with improved pharmacokinetic and safety profiles offer great potential for enhanced efficacy and better tolerability. This progress may ultimately pave the way for more effective mGluR-based treatments, providing renewed possibilities for individuals seeking relief from anxiety disorders.

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Section 2

Psychology

Chapter 2

Oncological Distress: Coping Styles in the Face of Suffering

Fabio Gabrielli and Floriana Irtelli

Abstract

Psycho-oncology explores some complex dimensions like emotions, feelings, and relationships of oncological patients. Cross-sectional studies have found that anxiety is a common reaction among cancer patients; it manifests itself with both mental (psychological) and physical (somatic) symptoms. As a matter of fact, many anxious patients suffer from a combination of mental and physical symptoms, with one aggravating the other, creating a vicious circle. Mental symptoms are worry, irritability, restlessness, insomnia, and nightmares. Physical symptoms consist of respiratory breathlessness, hyperactivity of the autonomic nervous system, or muscle tension. Depression is also very common as a reaction. In this regard, we must specify that coping styles act as early modulators of adaptation responses to the disease, and their advance knowledge can predict the person's response to the disease, and this can help to think about the most appropriate type of support to offer to the patient. It would be desirable to inform patients more frequently about the psychological consequences of cancer, about the psychological support available and its benefits, and about psychological interventions that can promote more suitable and effective coping.

Keywords: anxiety, psycho-oncology, coping, stress, oncological patient, relationships

1. Introduction

Psycho-oncology presents itself as a practice of care, in the light of a range of complex dimensions—emotions, feelings, gestures, postures, behaviors, relationships, and spiritual dynamics in relation to cancer patients [1]. Illness is always configured as the irruption of an extraordinary event into the ordinary, into everyday life, disrupting arrangements and experiences and reorienting priorities and values. Pain bears witness to the fact that man is not a machine and the doctor the one who repairs a fault in the system, but neither is pain a simple mechanism. If anything, pain refers to the complex relationship between man and the world and, at the same time, to a possible shattering, or at least a reorientation, of one's being, of one's way of opening up to life [2].

Man is open to a broad bundle of possibilities, as Heidegger writes in his Being most precisely this entity "The Dasein, the Being, the human" has the character of non-closure […] The Being is its openness [3].

The irruption of pain undermines the openness of the human being, its being an ever-open possibility, by shrinking or amputating these very possibilities and by disproportionately expanding the boundaries of anguish and despair.

Not only that, pain, for example cancer, often breaks in silently, and Leriche writes in this regard:

> *that in truth, most serious illnesses - - settle in without warning [...] When the pain arrives, it is too late. The end is virtually already there. It is imminent. The pain has only made an already compromised situation more painful and sadder. Defensive reaction against whom? Against what? Against cancer that usually only hurts when it kills? [4].*

Faced with the shrinking of life, of a pain that becomes lacerating after having been silent, one understands how what is at stake is the relational rupture between complex and closely linked worlds:

- Umwelt, the world of life cycles, of the law of nature;

- Uberwelt, the meaning we attribute to existence, its spiritual value;

- Eigenwelt, the world of the self and individual identity or 'me';

- Mitwelt, our being narrative, story, conversation with others, and the world (social relations) [5, 6].

The human complexity coagulated around pain, especially in the terminal phase, ends up, after all, by seeking an answer to the value of life, to its meaning if everything ends [3, 7, 8].

One understands therefore how approaching the suffering of the other requires extreme delicacy, a knowing how to live up to human experience. Therefore, in the practice of care, the physician is called to see in every suffering an unforeseeable event, an innumerable anthropological density. In the caring relationship, we are indeed called to see in the other, in every frailty, in every suffering. The flesh in which the scalpel sinks and the blood in which the drug flows are unique, unrepeatable; they are flesh and blood of a face that does not simply rely on the healer, on the doctor, on the clinical gaze; if anything, it requires that the doctor's expertise never forgets, not even for a single moment, that what I have in front of me has an inextinguishable dignity. The principle of fragility, in this sense, is the only one capable of binding human beings together: the sick person, in the full unfolding of his fragility, offers himself to the doctor, to his competent fragility, to his knowledge that is rooted in the hand that palpates, in the eye that scrutinizes, in the scalpel that incises and dissects, knowing, or at least trying to know, that they are fragile, fallible hands and eyes, at least not omnipotent [9, 10].

In order for the doctor to exercise the art of healing starting from the awareness of the uniqueness of each individual human being, it is necessary, especially in the case of oncological pathologies, to have a knowledge of the anthropological and psychological dynamics, of the languages, gestures, psychological traces, and defensive mechanisms that the sick person puts on stage.

2. Anxiety and illness

In a passage from Cicero, he specifies that there is a difference between anxiety and anguish [11] and emphasizes how anxiety is different from anguish, since those

who are anxious sometimes are not necessarily anxious, nor are those who are anxious always anxious. The passage is culturally interesting, since it refers, in our context, to a certain psychiatry that considers anxiety to be more related to the psychic contents of this emotion, to a circumscribed preoccupation, whereas it considers anguish to be more generalized and pervasive, less related to a single causal factor.

Anguish is a complex word, with a dense etymological and semantic track, the subject of a conspicuous philosophical tradition (think, just to name a few, of S. Kierkegaard, M. Heidegger, K. Jaspers, and J.-P. Sartre).

Anguish from a philosophical point of view is connected to the inevitability of pain in life; from an etymological point of view, we see that in the Greek language, the term refers back to the term Anánke, also connected to the Greek word anchein, 'to strangle' (see also the German Angst, 'anguish').

This etymological and semantic tracing refers, in turn, to the consonantal radical hnk: in the ancient Egyptian language, it includes meanings such as "cramped", "throat" (hng); in Coptic, we find it in the word "ring" (chalak), in Syriac in hnk, "chain", with the idea of suffocation implied [12, 13].

It is not by chance that Freud links the original sense of anguish (Angst, Enge) with the narrowing of breath experienced by the newborn at birth, to which it reacts with its first wailing, almost as if to indicate, already in coming into the world, a response of anguish to the danger underlying living itself [14].

Net of this pathway, then, anguish is constitutive of the human being and indicates a sense of suffocation, especially when pain breaks through, a narrowing of vital possibilities.

During illness, the sick person feels metaphorically suffocated; he feels that the bundle of possibilities that life has handed over to him is shrinking, that his existential path is increasingly narrow.

Great literature, whose purpose is to give voice to human experience, can never evade the discourse on illness, the burden of anguish it entails. Woolf rightly writes that considering the proportions of the spiritual change that illness produces, the virgin territories that it then opens up, it seems strange indeed that it does not figure, along with love, battles, jealousy, among the main themes of literature [15].

Thomas Mann, in The Magic Mountain, acutely notes how illness disrupts space and time, almost devouring them, and our very body, filled with anguish and suffering, produces a profound change in our place in the world [16].

We find this lacerating experience in an emblematic clinical case [17]: Paul was a 37-year-old single Caucasian graphic designer who was dying of acute lymphoblastic leukemia after two failed attempts at allogeneic bone marrow transplants (from identical nonfamily donors). He presented with acute pain and amplified anxiety, with chronic rejection disease affecting most of her body, accompanied by painful bloody sores. His steady gaze, like that of a deer dazzled by headlights, indicated that he was deathly afraid of his impending terminal condition. His tone of voice revealed an inner knowledge that the end was near but also the fact that he would have to suffer from this knowledge for days and weeks to come. Having to live with the thought of imminent death, alone in his hospital bed and covered in painful sores, triggered an unrelenting existential angst. Like many bone marrow transplant patients, Paul began to suffer from claustrophobia and panic attacks when he felt a strong sense of being 'trapped' and 'suffocated'. It became increasingly evident that this had less to do with being confined in isolation in his hospital room than with the overwhelming anguish he experienced when consciously confronted with his death. Paul referred to his terminal condition as 'a runaway train… heading off the track and towards a

precipice!' His intense death anxiety could barely be sedated by lorazepam or olanzapine. Paul finally found moments of respite by meaningfully exploring events in his life and sharing loose ends related to unfulfilled goals as a graphic designer or unrealized dreams such as finding love, getting married, and having children. It was as if meaningful dialogue and authentic self-expression allowed him to momentarily escape from his existential crisis of impending death and take part in a nostalgic and quiet space for a while [17].

In this context, psycho-oncology plays an important role.

3. Psycho-oncology: a complex discipline

The official history of psycho-oncology began in the mid-1970s in the United States. During this period, there was a decrease in the stigma associated with cancer, and more and more patients were being told directly about their diagnosis; thus began the study of emotional reactions to this event. Whereas initially the psychological problems of cancer patients and their families were addressed to nurses and social workers, the early research in this field led to an increasing referral to specialists such as psychiatrists, health psychologists (who focused on theoretical models of coping and cognitive-behavioral interventions), behavioral psychologists (who studied lifestyle changes, such as quitting smoking and diet modification to reduce the risk of cancer), and researchers in the nursing field (who dealt with symptom and pain management and control). Psycho-Oncology was immediately characterized as multidisciplinary [18]; the last few decades have seen its progressive affirmation and evolution. Today, Psycho-Oncology constitutes in the health field a reference for all those who, in the treatment of neoplastic disease, have a holistic vision of the patient, aimed at protecting and promoting a better quality of life for the patient, considering him/her in his/her complexity, given the inseparability in human beings of the biological component from the emotional one [19]. Currently, this discipline explores the psychological consequences of cancer for patients, their families, and carers; a further sphere of action concerns research aimed at elucidating the possible relationships between psyche and soma with regard to the pathogenesis of tumors, their evolution, perhaps even some possible 'spontaneous cures' or, conversely, dramatic worsening [20]. It therefore stands as an important link in the integration of the psychic and somatic disciplines in dealing with a pathology that is so vast, multifactorial, and, in some ways, so obscure. This integration is also intrinsic in the etymology of the term: 'Psycho' derives from the Greek word 'psyche', meaning mind or soul, while 'Oncology' derives from the Greek word 'Onkos', meaning mass, and means the study of tumors. 'Psycho-Oncology' therefore has to do with the relationship between the tumor, the body, and the mind. An important part of 'Psycho-Oncology' today is 'Social Psycho-Oncology,' which also includes the broader idea that cancer affects not only individuals but also their families, friends, and colleagues, as well as the society in which they live. The psycho-social implications of the disease are therefore also fundamental [20]. The main objectives of this discipline are respect for life and the human person and the family and cohabiting units, the right to the protection of relationships and affections, the consideration and treatment of pain, and psychological support in the different stages of the illness [19]. Specifically, the central themes in patient care focus on existential anxieties and anxieties, such as the concern to maintain one's own identity, to find meaning in one's own life experience, to respond to transcendent and spiritual themes, and to maintain hope [21]; thus, both the assistance to the person

affected by cancer and the care pathways must be articulated taking into account, in a comprehensive manner, all the dimensions of human existence. This perspective is rooted far back in the history of medicine; in this perspective, George Engel introduced the term 'Biopsychosocial Approach' as a privileged modality both to decode and understand health and disease processes along the entire existential pathway and to articulate forms of care and taking charge. The biopsychosocial model is inspired by the complexity paradigm, in clear opposition to biomedical reductionism, as well as to the hierarchization of sciences. It adopts the perspective of the general systems theory developed by Von Bertalanffy, which considers a set of interrelated events as a system, which manifests specific functions and properties depending on the level at which it is placed in relation to a broader system comprising it. Systems theory argues that all levels of the organization are connected to each other so that a change in one affects change in the other, mitigating the dichotomy between holism and reductionism [22]. Overall, the model refers to three basic principles: dialogue-connection, relationship, and humility. In other words, it aspires to look at the person as a 'whole' as a genetic heir (bio), a subject of reflection and decision (psycho), as well as a cultural-historical and family (social) subject. The axioms of the model are inclusive (understanding of diversity) and nonexclusive (setting aside what is deemed as not being one's own competence), whose responses are comprehensive and global whatever the point of entry into the system (now biological, now psychological, now social). In Psycho-Oncology, the centrality of this model has been confirmed and validated by a scientific literature, now boundless, which marks the transition from a traditional medical model centered on the body (and on the disease as a purely biological event) to a person-centered medicine [23], and it is now a widespread awareness that a biopsychosocial screening, rather than a compartmentalized approach of medical and psychosocial models, can help the planning of a more effective treatment and help an early and useful management of distress [24, 25].

4. Eustress and distress

The term stress was introduced into the field of psychology by Seyle. He was the first to use the term stress to describe a range of physical and psychological responses to adverse conditions or influences [26]. Originally, 'just being sick' syndrome covered an organism's stereotypical response to a wide range of physical, biological, or chemical stimuli. Later, looking for a term to represent this response, Seyle used the word 'stress'. Stress is an English term meaning 'pressure' and was introduced by analogy with engineering, where it is used to refer to any force that is applied to a body to test its endurance under stress. With time, this term was then also used to indicate more specifically 'a state of non-specific tension in living matter, manifested by tangible morphological transformations in various organs, and particularly in the endocrine glands that are under the control of the pituitary gland' [27]. The term stress, which describes the reaction on the part of the organism, is distinguished from stressor (stressful event, or stressor), a term that describes the stimulus factors that cause the aforementioned reaction on the part of the organism. Stressors can be serious factors (the death of a loved one or a serious illness), minor factors (minor facts of everyday life), acute factors (accidents), and chronic factors (e.g. a highly competitive work environment) [28]. Seyle also distinguished between eustress (or good stress) and distress; they were originally included in the broader definition of stress but were immediately referred to as distinct from each other. Seyle asserted that

stress is an inevitable consequence of living, but distress appears when the demands made on a person (in both their psychological and physiological aspects) overwhelm the capacities and energies the person can and believes he or she can expend in maintaining homeostasis. The stimulus-demand may therefore have a more or less welcome meaning [29]. This idea was well illustrated by Holmes and Rahe [30] in their construction of the "Social Readjustment Rating Scale": every stress can be classified into eustress and distress, the former is caused by a demand considered disproportionate in magnitude, while eustress is caused by a demand considered acceptable, which creates a moderate and not excessive level of tension that allows one to cope successfully with demands. This, however, is only one aspect of eustress. The concept of an optimal stress level derives from the studies of Yerkes and Dodson [31] who explained how increasing stress is beneficial for performance as long as it is moderate, after which performance will deteriorate. In order to clarify the connection between Yerkes and Dodson's theory and Seyle's, it must be explained that the nature of each stimulus depends on how each individual interprets it and chooses to react to it. It depends on the individual whether a stress will be eustress or distress. Eustress is the primary result of a positive perception of the stressor, whereas distress is the result of a negative perception. The classification therefore depends on what the stressor represents to the individual, what value is attached to it. Seyle suggested that learning to respond to stressful stimuli with positive emotions, such as hope, maximizes eustress and minimizes distress, while responding with negative emotions, such as despair, greatly increases distress [29]. In the perception of the stressor, and the attribution of meaning to it, the characteristics of the individual intervene: presenting an internal locus of control (and self-efficacy) has quite different implications than an external locus of control. Self-efficacy is the belief that one is able to control environmental challenges by taking adaptive action, and in accordance with social cognitive theory [32], self-efficacy in the case of cancer strongly influences behavior and is positively associated with adaptation [33]; it correlates with active coping and negatively with passive coping [34]. It is Seyle himself who also introduced the notion of the 'general adaptation syndrome' to describe the way in which the organism copes with stressful events; he distinguishes three phases that follow one another in this order:

1. Alarm phase: the autonomic nervous system is activated in the face of intense stressful events;

2. Resistance phase: the organism adapts to stress, and, if the stress is too intense, there are transitory manifestations such as enlarged adrenal glands, gastrointestinal ulcers, etc.;

3. Exhaustion phase: if the stressor persists, or if the organism is unable to mount adequate responses, the organism goes into irreversible responses, including death.

On the other hand, it is to the credit of the scientist Lazarus that he has integrated Seyle's model with the more purely cognitive aspects connected to the subjective processing carried out by the person regarding the specific stressors, creating a more complex model. As a matter of fact, the same event, as already mentioned, may have different meanings for different individuals, and when faced with unequivocally stressful factors, different people react in different ways and with different outcomes. Optimal adaptation requires reaction strategies that are active as well as multiple, flexible, and calibrated to the specifics of the stressful factors or events at play.

The stress response is thus modulated in two ways by the psychological characteristics of the person: in the phase of perception and processing of stressful factors and in the phase of coping with these factors. The characteristics that intervene at this second level and modulate stress reaction strategies are called coping Skills, and the entire process of reacting to and coping with stress is referred to by the term coping [35], an English-speaking term that literally means 'holding one's own,' 'fighting successfully'. Awareness has grown since the 1960s that while stress is an inevitable aspect of the human condition, coping makes a big difference to the outcome of coping with it [36]. Today, referring to the Psycho-Oncological context, for coping, we globally mean the cognitive and behavioral style of an individual in dealing with the pathology, that is, the ability to face problems and their emotional consequences, and refer to the adaptation of individual [37]. This construct has proved to be truly fundamental in complex disease situations such as cancer. Among its various meanings, it is considered as a sequential series of stressful events: diagnosis, aggressive treatments, fear of death, and changes in social and physical context. Each of these events already represents severe stress in itself [38]. In this context, the concept of coping represents a parameter capable of exerting a considerable influence on the different modes of psychological reaction and psychosocial adaptation to the disease, on possible psychopathological complications, on the quality of life following diagnosis, on compliance with antineoplastic treatments, and on the biological course of the disease. The patient's ability to face a possible situation of existential crisis, triggered by the neoplasm, depends on a well-codified series of factors. According to Lazarus and Folkman [35], the psychological impact of a stressor is influenced both by the characteristics of the individual and by the characteristics of the stressor. With regard to the characteristics of the stressor, we must therefore take into account the type of pathology (symptomatology, course, therapy, collaterals); regarding the characteristics of the individual, they turn out to be complex, multiple, and strongly intertwined with each other: the level of adaptation prior to the neoplasm (for example, in relation to previous situations of illness); the meaning attributed to the disease, which in turn depends on self-efficacy, the history of the subject, his personality, and cultural and religious factors; the psychological attitude of the patient (age, degree of psychological maturation, introspective ability, education, any psychiatric disorders); and, above all, the coping style [34]. Also important is the type and extent of social support that the person can take advantage of [39]. For prognostic purposes, the personal meaning that each patient attributes to the disease is of particular importance, and according to Lipowsky, there would be eight different possible meanings attributable to the diagnosis of cancer: disease understood as punishment, as an enemy to fight against, as loss of one's sexual identity or professional value, as a challenge to one's own mental resources, as a strategy, as a relief in patients who had already reduced their expectations toward life, and as organ weakness [40]. The consequences of this attribution of meanings are decisive: if the disease is perceived and interpreted as a punishment, reaction models in which guilt prevails can be activated, with consequent behaviors of fatalism and resignation; if the perception prevails that cancer is an unwelcome guest or an enemy not to be given space because life is very important, the modalities that emerge will be characterized by acceptance of the challenge, open struggle, and will not to give up; if the perception prevails that the illness will lead to estrangement from loved ones, dependency behaviors and the need for continuous reassurance may be put in place [19]. Weisman [41] discussed the two main aspects of experiencing cancer in the 1970s: coping and vulnerability. In his studies, the so-called "Good Copers" have the persistent belief that they will be able to

deal with the disease, are practical, and directly address the issues; the "Bad Copers" are characterized by regret and pessimism. Vulnerability is divided into dysphoric and dispositional types. The first is based on patients who report current experiences and depressive symptoms; the second reflects underlying character dynamics, which lead to alienation, annihilation, and despair [25]; therefore, there is a coping model toward oncological disease that takes into account the existential vulnerabilities associated with the diagnosis. He identified four phases:

1. Life Situation: This includes the impact of diagnosis, dealing with death, and anxieties about the future. There is hope for a cure in this phase.

2. Adaptation and Mitigation: There are varying levels of impairment, and the focus is on the pragmatic aspects of the treatment and its effects. At this point, the sense of having changed becomes stronger. The characteristic activity of this stage is vigilance. Patients who are being treated may not continue after this stage.

3. Relapse and Recurrence: At this point, existential concerns are evoked, and it may be more difficult to express optimism. The patient's goal is often to maintain control.

4. Deterioration and Decline: This involves a consistent deterioration in functional abilities, a sense of time being limited, and variable attitudes, but often, there is a tendency to stop dwelling on details and focus on palliative care [25, 41].

5. Coping styles and adaptation to illness

Coping styles have been classified hierarchically by Greer according to their influence on the survival of cancer patients: on the basis of the results obtained, the author placed the combative coping style in the first position, in second, the avoidance-denial; instead, the effects of fatalism turned out to be worse, and those of anxious concern and despair proved to be worst [42–45].
We will therefore present them in this order:

- Combativeness: This style is characterized by the patient's acceptance of the challenge of defeating the disease; in the words of the creators of this dimension, Greer and Moorey, 'the patient sees the diagnosis as a challenge, has an optimistic view of the future, believes that it is possible to exert control over the disease.' The patient manifests coping responses aimed at direct confrontation; those who adopt this strategy therefore have an internal locus of control and want to know as much as possible about their disease, ask for input in the choice of therapies, adhere to the proposed treatments, participate in the proposed complementary interventions, and make changes to their lifestyle in order to preserve their health, for example, by changing their diet and exercising [20]; this strategy can be defined as active, positive coping, as it represents the tendency to actively confront and face the disease [20, 46]. It can also be associated both in the short and in the long term with adaptation denial, which protects against anxiety and depression and is expressed in the tendency to minimize the seriousness of the situation and in the lively hope of success in the battle against cancer [20, 47]. The optimism that characterizes this coping style has beneficial effects on the

health, well-being, and quality of life of those who adopt it. Importantly, the coping style itself mediates the positive effect of optimism on quality of life and emotional, cognitive, and social functioning. Combative coping mediates these effects positively while fatalism, anxious concern, and despair, negatively: it is therefore not enough to be optimistic if you do not adopt a combative coping style. Combativity brings with it lower levels of anxiety and demoralization and responses of confrontation and conviction of at least partial control over events [19]. To refer to the construct "Mental Adjustment to Cancer," patients who face the unfortunate event with a fighting spirit use comparison responses that can be summarized with the statements: "I see this disease as a challenge," "I am determined to defeat the tumor," "I am very optimistic;" they adopt more flexible and differentiated cognitive and behavioral strategies, "I am actively trying to improve my health," which favor a more positive view of the event, without reducing its potential danger, even leading to grasping a deeper meaning of existence. As a result, as already introduced, this style is associated with less psychological morbidity, a feeling of greater personal control over the state of one's health, and a more favorable course of the disease, therefore a greater survival from it [25].

- Avoidance-Denial: This strategy is very complex and is generally characterized by the tendency to avoid dealing directly with all issues related to the illness, the use of euphemisms to talk about it, and is linked to the use of the denial defense mechanism (avoidance of seeing unpleasant aspects of the illness). This is very common and often has a useful effect in protecting against anxiety but can cause problems if used as the only form of defense and if taken to extremes. A high level of avoidance, used as the sole coping strategy, can also lead to unrealistic self-efficacy perceptions and alexithymia [25]. Avoidance has however been found to be correlated with poor adaptation to the illness [48].

- Fatalism: This is a strategy characterized by a fatalistic attitude of resignation and passive acceptance of the illness, a belief in a lack of control over events and resigned acceptance of what fate has determined: those who adopt this strategy recognize the seriousness of the situation but accept it as their fate. We must therefore point out that the tendency to perceive external events as being linked to fate, to destiny, is typical of those who have an external locus of control, and this encourages poor adaptation to illness and a lack of responsibility for one's own state of health [19]. Recent research has shown that it correlates with higher levels of distress 1 year after surgery; it has also been shown that fatalism particularly correlates with despair and has negative psychological effects throughout the course of the disease: it correlates negatively with optimism at the time of diagnosis, mediating negatively its effect on Global Heath Quality of Life (GHQOL), with GHQOL before and after surgery, and with emotional functioning before surgery. The resignation that fatalism entails is positively correlated with high levels of anxiety and depression; they were also found to be positively correlated with feelings of hopelessness, characteristic of the 'coping style' hopelessness [25].

- Anxious preoccupation: This is a strategy characterized by constant worry about illness and feelings of danger, a high proportion of anxiety and depression, and the placing of illness at the center of one's existence. It was found to be negatively correlated with social and emotional functioning. Those who adopt this coping style are constantly seeking reassurance, requesting visits, or, on the contrary,

escaping from the care setting because it is too distressing [19]. In this regard, it has been particularly highlighted how the continuation of this coping style negatively affects patients' survival time, even 10 years after diagnosis. It was then shown how this strategy fortunately decreases after the first few months after diagnosis. It was finally found to be positively correlated with the coping style despair and fatalism [25].

- Hopelessness: This is characterized by feelings of defeat and the feeling of being overwhelmed by the diagnosis, a pessimistic attitude toward the disease [46, 49]; it is related to high levels of anxiety and depression, poor cognitive strategies, and the belief that one has little control about events. There is also poor therapeutic adherence and an attitude of renunciation: the arrival of the disease is proposed as an event that leaves no way out, impeding the search for help and the planning of any intervention [19]; as a matter of fact, there is a correspondence between despair and demoralization: affective symptoms of existential distress, loss of meaning and life goals, cognitive propensity to pessimism, sense of personal failure, lack of motivation to face the event differently, sense of social isolation, and alienation [25].

6. Dyadic coping

Starting from the evidence that patients with cancer and their loved ones (particularly the companion) are hit jointly by the stress of this disease, several researches about coping have investigated how partners can cope together with stress and how the dyads attempt to cope mutually influence each other [50, 51]. An evolution coping research us the focus on concept of dyadic coping [52], which is the way to deal together with the disease; it considers the stress experience at a dyadic couple level and the mutual influence process, in which one partner's stress can influence the other one. This concept emphasizes that there is an interdependence between social support and coping styles: the coping success is strongly linked to other significant ones responses [52]. Bodenmann studied dyadic stress and created a specific dyadic coping process theory. He defined dyadic stress as a distinct form of social stress, which includes common concerns and emotional intimacy between two persons. Specifically, it is relevant that a stressful event always affects both partners indirectly and directly. The dyadic coping is part of an interpersonal process that involves both partners [53–56], and it is rooted on Lazarus and Folkman transactional stress theory [35, 36] but expands it with some process-oriented and systemic dimensions. Starting from the question "How does stress affect marriage? How does dyadic coping can influence the relationship between stress and the quality of married life?," Bodenmann has distinguished between negative and positive dyadic coping. Among the positive dyadic forms, there are:

a. Delegate Dyadic Coping: One of the partners is asked to assume more responsibility for trying to reduce the tension of the other, and the partner accepts.

b. Supportive Dyadic Coping: One partner supports the other in her/his attempts to cope. It can be expressed through acts such as assisting others, solidarity, empathic listening, and the purpose of reducing partner's stress.

   c. Common Dyadic Coping: Both partners participate in the coping process more or less in a complementary way, implementing common problem solving and common research for information.

Among the negative forms of dyadic coping, we can find:

   a. Ambivalent Dyadic Coping: A partner provides unwilling support or a support with the belief that it will be useless.

   b. Superficial Dyadic Coping: It is not sincere support (for example, it is expressed as trying to support the partner without empathy).

   c. Hostile Dyadic Coping: The support is provided accompanied by minimization, sarcasm, and interpersonal distance [25].

Specifically, Acitelli and Badr [57] studied dyadic coping in the cases of chronic illness, such as oncologic pathology; they investigated the difference in the behavior of men and women and different expectations (depending on the gender) toward the partner. The data obtained from these researches show that the chronic disease should not be interpreted as an individual challenge but as a relational challenge; as a matter of fact, it emerged that if the partners communicate appropriately about their relationship, their health will hardly affect their marital satisfaction, especially for women: specifically, the more husbands are involved in a dialogue with the sick wives, the more satisfaction there will be for their relationship with their wives. Women, with their interdependent approach to relationships, are more likely to pay attention to these elements and derive good consequences for their relationship satisfaction.

On the contrary, it has been noted that if the oncological partner has great emotional needs and the healthy partner acts in accordance with the traditional gender role, sick women suffer more than men in the same conditions. Female subjects, on the other hand, in the role of the healthy partner tend more to give emotional support through dialogue, and it has been verified that the more husbands talk about their relationship, the more this generates support and favors a positive outcome. Acitelli and Badr [57] have also highlighted how perceiving the disease as "our disease," rather than "my illness," has significant implications on perceived social support and coping: it is better for the couple's well-being to understand oncologic situation as a topic of the relationship, rather than as a purely individual matter; this leads to approach the situation like a team that solves the problems together, thus reporting a better adaptation [25, 57].

7. Conclusion

Fear of suffering, death, and the unknown are just some of the many experiences that the cancer patient has to deal with on a day-to-day basis, and many of the psychological effects of cancer must be considered, indeed, in terms of a reaction to the loss or the risk of the future loss of health and its implications. What consequences does this have for the cancer patient's mind? Cross-sectional studies have found that anxiety is a common reaction among cancer patients; it manifests itself with both mental (psychological) and physical (somatic) symptoms. As a matter of fact, many anxious patients suffer from a combination of mental and physical symptoms, with

one aggravating the other, creating a vicious circle. Mental symptoms are worry, irritability, restlessness, insomnia, and nightmares. Physical symptoms consist of respiratory breathlessness, hyperactivity of the autonomic nervous system, or muscle tension. Depression is also very common as a reaction [19, 25]. In this regard, we must specify that coping styles act as early modulators of adaptation responses to the disease, and their advance knowledge can predict the person's response to the disease [58] and help think about the most appropriate type of support to offer. Patients at "high risk" of emotional distress do not show more problems than others but more inadequate ways of dealing with them (such as anxiety and resignation) and an inability to produce an alternative set of coping strategies. "Low risk" patients have an active, flexible, and differentiated coping style, characterized by methods of confrontation, redefinition of problems, and compliance with authority. In general, strategies characterized by a more efficient and diversified way of coping with problems, compared to those that are more passive and characterized by feelings of hopelessness and helplessness, are more effective for better adaptation [19]. In particular, subjects who face the unfortunate event with a fighting spirit use comparison responses that can be summarized with the statement "I see this disease as a challenge" and adopt more flexible and differentiated cognitive and behavioral strategies ("I am actively trying to improve my health"), which favor a more positive vision of the event, without reducing its potential danger, even leading to grasping a deeper meaning of existence. As a result, this style is associated with less psychological morbidity, a feeling of greater personal control over one's health, a greater quality of life, and, according to some authors, a more favorable course of the disease [49, 59]. Understanding the type and effectiveness of the individual and dyadic coping styles with which one deals with the disease takes on particular importance in this perspective: if they are functional and effective, then adaptation to the disease can also turn into personal growth. On the contrary, if the type of situation is interpreted as too stressful, there are too high levels of anxiety, and therefore, the onset of psychopathological reactions and a state of intense subjective suffering are possible [38]. Personality variables (such as dominance and interpersonal trust) and the related processes of appraisal and coping have, in turn, a significant relationship with psychological symptoms and adaptation [25]. Among the psychological aspects that influence the coping style, there are aspects relating to individual history and personality characteristics. As already anticipated, the tendency to perceive external events as ineluctably linked to destiny (external locus of control) tends to favor maladaptive ways of approaching the disease, while the tendency to perceive events as at least partially controllable (internal locus of control) facilitates more adaptive ways. Furthermore, people with personality disorders or with inflexible psychological defenses and rigid ways of relating to reality are patients at risk of psychopathological complications. In this regard, the patient's previous level of adaptation (depending on the number and severity of previous life events, negative or positive family, or personal experiences) is also significantly associated with the cancer coping style. The moment in the patient's life when the disease appears also obviously plays an important role as it modulates the degree to which the disease interferes with developmental goals [19]. Upstream knowledge of individual and dyadic coping styles is very important in oncological clinical practice, for example, the relational implications and the ways of relating that the professional figure should adopt in the case of a patient who wishes to have detailed information in order to deal with these, compared with one who prefers to leave the management of his problems to the other. It should be pointed out that given that cancer patients experience significant levels of anxiety and depression, it is to be hoped that in the

future, there will be an increasing emphasis on the need to screen patients' emotional functioning, distress, and their desire to receive psychological support [25]. It would also be desirable to inform patients and caregivers more frequently about the psychological consequences of cancer, about the psychological support available and its benefits, and about psychological interventions that can promote more suitable and effective coping, since resilience in the case of cancer pathology can be improved through psychological intervention [60]. Finally, it should be remembered once again that oncological pathology can have relational repercussions, and therefore, stress can occur both for the patient's caregivers and for those who have a medical role in the treatment; therefore, specific support interventions can be appropriately proposed not only for the oncological patient but also for his family and for the care team; the latter can also be negatively influenced by a possible death of the patient; and therefore, it makes sense to propose specific interventions in these cases.

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Chapter 3

Theory for Anxiety Disorders

Jorge Garza-Ulloa

Abstract

"Anxiety" is part of our lives and is frequently generated by unhandled stress, but people with "anxiety disorders" have repetitive episodes of excessive "anguish" and "anxiety" that interfere with their daily activities. At the present time, the causes of "anxiety disorders" are not fully understood as diseases, where doctors can diagnose or evaluate the level of diseases using mainly medical lab tests or biomedical imaging, identifying the cause as infection, inflammation, or other physical factors that can be treated with medication or surgery or even prevented by vaccines. Based on the logical assertion that "in order for something to be improved, it must be understood and measured". The objective of the "theory of anxiety disorder" is to understand it and identify body parameters that can be measured in a "subjective mode", and I recommend some new experimental "objective mode", to detect the degree of physical altered symptoms and mental abnormal reactions classified as "anxiety disorder", which is characterized by a consistent sense of feeling pressured and overwhelmed. The steps to understanding the process by which "anxiety" is generated and how it could be analyzed and measured as evolving into "anxiety disorder".

Keywords: anxiety, anguish, emotion, anxiety disorder, hormones, neurotransmitters, HP-axis

1. Introduction

The "anxiety" process usually begins with "anguish", which is an "emotional distress" or emotional suffering or emotional pain that causes physiological emotions such as "fear", sorrow, and others. These emotions generate a mental state identified as "stress" that shows strain in adverse situations. "Anxiety" includes a wide range of symptoms that are usually temporary, showing a mental condition with excessive nervousness about imminent threats that could be real or just perceived, leading to avoidance behaviors, and showing evidence of physical symptoms such as muscle tension, increased heart rate, and others. "Anxiety" is a normal reaction for natural survival, but when this process is repetitive, it opens up for "stress accumulation" symptoms, that could evolve over time into "anxiety disorder". Which is an extremely debilitating mind state with excessive fear, negative behavioral and emotional consequences that frequently detect false threats that make the body spend unreasonable energy levels on something that is not really a threat [1].

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When we feel afraid of a present situation, "emotional distress" is generated as "anguish", the body reacts, showing "physical emotion" as fear, and "emotional strain by the adverse situation" is observed as "stress" symptoms. Occasional "stress" is known as "acute stress," presenting dramatic physiological and psychological reactions for a short-term period of time. To handle the situation, our brain releases a group of "hormones" identified as "stress hormones." They regulate the process and handle the affection index and severity degrees of the process that our brain relates with memory mechanisms to modulate consolidation and retrieval processes associated with past emotional episodic events that were stored in memory, such as fear and extinction situations that were already learned. When these fearful situations are repeated constantly, the process is altered, showing longer durations, creating "stress accumulation", identified as "chronic stress". That constantly alters our "nervous neuron system" with processes that are evaluated constantly as "excitatory and/or inhibitory state changes," presenting physical altered symptoms and mind abnormal reactions classified as "anxiety disorder," characterized by a consistent sense of feeling pressured and overwhelmed.

2. "Anxiety disorder"

"Disorder" is a collection of symptoms that come together to alter the mental health condition and disrupt how the human mind works. At the present time, the causes of "anxiety disorders" are not fully understood as diseases, where doctors can diagnose or evaluate the level of disease using mainly medical lab-tests or biomedical imaging, identifying the cause as infection, inflammation, or other physical factors that can be treated with medication or surgery or even prevented by vaccines. Diagnosing or evaluating "anxiety disorders" is not an easy task, even for doctors. Frequently, the primary care provider, the one that checks for "anxiety disorder" signs and, if he suspects some of them, generates a patient reference to a mental health specialist such as a "psychiatrist or psychologist" to confirm or not the disorder. They must evaluate and identify the kind of "stress", that is divided into three main categories: "anxiety related disorders", "obsessive-compulsive, and related disorders," and "trauma- and stressor-related disorders" [2]. That is characterized as follows:

- "Anxiety related disorders" with sense of excessive fear, with emotional responses to actual perceived threats and/or future ones. Presenting negative behaviors with emotional consequences.

- "Obsessive-compulsive, and related disorders" with persistent intrusive thoughts known as obsessions triggering compulsive behaviors of "anxiety".

- "Trauma- and stressor-related disorders" are closely related to traumatic experiences in his or her life.

And if possible, find the reason as "specific phobia", "social anxiety disorder (SAD)", "panic anxiety disorder", "post-traumatic stress disorder (PTSD)", "generalized anxiety disorder (GAD)", and many others. The medical diagnoses by specialists are based on five main types of analysis: "assessment evaluations", "anxiety physical

symptoms", "medical history review", "current prescriptions", and "lab-tests and/or biomedical imaging". Where each one can be described as:

1. "Assessment evaluation," which are psychological questionnaires to evaluate the mental health of the patients, many doctors use the standard criteria: "Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published by the American Psychiatric Association" [3].

> "Assessment evaluations" are in "subjective mode," where the responses depend on each patient's point of view, as opposed to "objective mode," as lab-tests are measured values.

2. "Anxiety physical symptoms," evaluating each of them and paying special attention to recurrent events that last for a longer time than normal, such as restlessness, nausea or digestive troubles, muscle contractions, palpitations, cold or sweaty hands, compression of nerves in hands or feet, shortness of breath, increased heart rate, high blood pressure, dry mouth, hot flashes or chills, essential tremors, stomach pain, sleep problems, weakness, or fatigue, and special focuses on avoidance of situations that may cause "anguish" emotions such as "fear" and many others.

> "Anxiety physical symptoms" where only some of them are under "objective mode", and others are under "subjective mode". The main problem is that many "anxiety symptoms" are very similar to those of other illnesses and/or diseases.

3. "Medical history review" to detect body changes through time such as weight, heart rate, blood pressure, illness, diseases, injuries, etc.

> "Medical history" is recommended to review to find physical or mental changes in the past.

4. "Current prescriptions" that are taken to analysis their interactions and possibility to develop "anxiety" symptoms.

> "Doctors have access to many electronic databases online that are continuously updated, including new medication uses and dosing, regimens for drug interactions, drug allergies, and duplicate therapies, helping them to ensure accurate medication doses.

5. "Lab-tests and/or biomedical imaging" to detect other illnesses or body lesions as possible causes for "anxiety" to eliminate the possibility of them having similar symptoms as:

    a. "Postural Orthostatic Tachycardia Syndrome" (POTS) is an autonomic system disorder that increases heart rate (tachycardia) and often drops blood pressure upon standing [4].

b. "Endometriosis" is a women's disease with chronic pain in the lower back and pelvis, bowel movements, urinating after sex activity or in menstrual periods, and other activities presenting frequently other symptoms as fatigue, anxious mood, depression, and others [5].

c. "Crohn's Disease," also known as inflammatory bowel disease (IBD), is observed as digestive tract inflammation, mainly in the small and large intestine, with symptoms of diarrhea, fatigue, stool blood, and others [6].

d. "Fibromyalgia disorder" presents generalized muscle pain, joints, and nerves with symptoms of fatigue, cognitive problems, sleep disturbances, anxiety, depression, and others [7].

e. "Hyperthyroidism" happens when the thyroid gland fails to produce thyroid hormone, presenting symptoms of poor concentration, tiredness, muscle weakness, and others such as fatigue, weight gain, cold intolerance, and others [8].

f. "Addison's disease," also known as "adrenal insufficiency" of the hormone cortisol, happens when the adrenal glands do not produce normal cortisol levels. Low cortisol levels can actually cause anxiety and depression [9].

g. "Ankylosing spondylitis" is a type of arthritis that affects the spine and large joints with inflammation, causing pain in the ribs and shoulders, damaging the joint between the spine and the hipbone, and also causing bone bridges between vertebrae in the spine, fusing those bones. "Ankylosing spondylitis" mimics pain from a panic attack [10].

h. "Pseudo bulbar affect disorder (PBA)" that is characterized by episodes of sudden emotions of crying/laughing without control. This disorder if frequently a symptom of neurologic diseases [11]

And many others neurologic diseases as "Parkinsonism*," "Alzheimer's", and many others that may include "anxiety" as one of their collection of symptoms.

Note*: "Parkinsonism" is a nervous system disorder that affects areas of the brain that process body movements. It worsens with time with symptoms such as slowed movements, tremors, rigidity, stiffness, shaking in upper and lower limbs, and others with symptoms such as unbalanced walking gait, freezing, stooped posture, and many more.

3. Theory for anxiety disorder- general overview

"Theory for Anxiety Disorder," seen in a general way, can be explained in two chain reactions: "anxiety" and "anxiety disorder," as shown in **Figure 1**.

- "Anxiety" is a normal chain reaction of internal processes for natural convenience when there is a threat event, as indicated in **Figure 1a**. It begins with
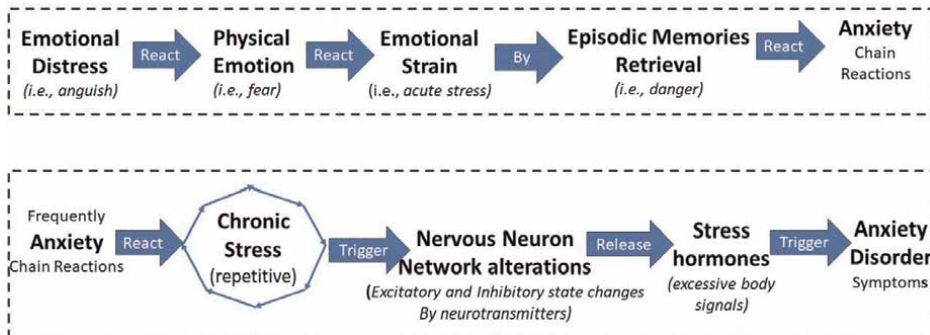
Figure 1.
The "Theory for Anxiety Disorders-General Overview" can be explained in two chain reactions: (a) "anxiety" normal process for natural supervenience as shown in the top secction, and (b) "Theory for Anxiety Disorder" explain the sense of feeling pressured and overwhelmed as a result of frequent "anxiety" chain reaction as shown in the bottom section.

emotional distress as "anguish", reacts with physical emotion as "fear", and reacts with emotional strain from adverse situations as "acute stress". That process involves the "retrieval of episodic memories" of danger that reacts with "anxiety", which is expressed with mind and body symptoms alterations.

- "Anxiety disorder" is another chain reaction based on repetitive thoughts of being under threat, showing a sense of feeling pressured and overwhelmed for frequent mind evaluation of the "anxiety" chain reaction as indicated in **Figure 1b**. It usually begins with a sequence of events and reactions that are frequently analyzed. They evolved as a kind of "stress accumulation" identified as "chronic stress" characterized by longer episodes, due to the frequent alterations of neuronal network stability, that continuously evaluate how to handle the nervous neuron network alterations, by excitatory and inhibitory neurotransmitter signals that could request excessive secretion of "stress hormones" to stabilize the body and mind alterations that are reflecting in the human body with a wide range of symptoms of a physical reaction with a mental condition that indicates excessive nervousness about imminent threats, that could be real or just mentally perceived as "Anxiety Disorder".

> The physical and mental chain reactions of frequently "anxiety" are generally explained by the "Theory for Anxiety Disorder-General Overview", resulting in the expression of the sense of feeling pressured and overwhelmed by frequently "anxiety" chain reactions events that are shown externally with physical body alterations and mind abnormal responses triggered by fast changes on the neuronal network's stability neurotransmitters expressing the excessive "stress hormones" involved in the process for stabilizing the series of frequently threats.

4. Theory for anxiety disorder: details overview

To understand the "Theory for Anxiety Disorder: Details Overview" it is necessary to document all the elements and actions involved in the "anxiety chain reaction" and how it evolves into an "anxiety disorder chain reaction". These elements are organized

on: "chemical messenger types", "endocrine system glands that release stress hormone", "neurotransmitters involve handling stress and anxiety", "the endocrine system and stress hormone system", "HPA axis loops," and "the theory for anxiety disorder: details overview."

4.1 Chemical messenger types

The human organism is composed of "living cells," and extracellular body cells are the physical substance of organic materials organized into tissues, organs, and systems. The body's "living cells" detect the activity around them and respond in real time, sending and receiving millions of messages using "chemical signals" generally known as "chemical messengers." These are proteins or other types of molecules that are often secreted from the cell and released into the "extracellular space," which can be close or not. Each "chemical signal molecule" is received only by the right "receptor cells" for that specific signal. When the specific "chemical signal" reaches the right receptor, it binds into the "receptor cell". This process is known as "ligand", and it triggers a change inside the "receptor cell".

> In other words, "intercellular signals between-cells" are converted into "intracellular signals within cells" that trigger a response.

Generally, there are four categories of "chemical signal messenger" according to the distance that the signal travels through the organism to reach the "receptor cell", These are: "autocrine", "paracrine", "endocrine", and "neurotransmitter". Each category can be described as follows:

- "Autocrine chemical messenger" stimulates the cell that originally secreted it. i.e., "white blood cells (WBC)" secreted during an infection.

> Many types of WBCs can stimulate their own replication to rapidly increase the total number of them.

- "Paracrine chemical messenger" acts locally on nearby cells into the extracellular fluid that affects surrounding "receptor cells" i.e., "Histamine" released by certain WBC types.

> The histamine released by WBC during allergic reactions stimulates vasodilation in nearby blood cells.

- "Endocrine chemical messengers" are secreted into the bloodstream by certain glands and cells as a part of the "endocrine system".

> "Endocrine chemical messengers" travel through the "circulatory system" to reach their "target cells".

- "Neurotransmitter chemical messengers" are secreted by "nerve cells or neurons" that activate other adjacent "neurons," "muscle cells," or "glandular cells."

> "Neurotransmitter chemical messengers" are secreted into a "synaptic cleft" in a synapse chemical environment at the end of the neuron cell that connects to other neurons.

In this research book chapter, we focus especially on "endocrine chemical messengers" and "neurotransmitter chemical messengers". Where:

- "Endocrine chemical messengers" are special "hormones" that are secreted by glands as a part of the "endocrine system" into the bloodstream, i.e., "adrenal glands" and released into the bloodstream to act on their specific "target cells",

- "Neurotransmitter chemical messengers" that are produced by the brain's glands as a part of the "autonomic nervous system (ANS)". They are molecules used by the ANS to transmit messages between neurons (nervous cells) or neurons to muscles. The place for communication between two connected neurons is the "synaptic cleft", which is a small gap between neurons that is commonly known as a "synapse," as shown in **Figure 2b**.

> "ANS" regulates the body's internal environment with specific functions without conscious control, such as respiration, circulation, digestion, body temperature, metabolism, sweating, and many other internal functions.
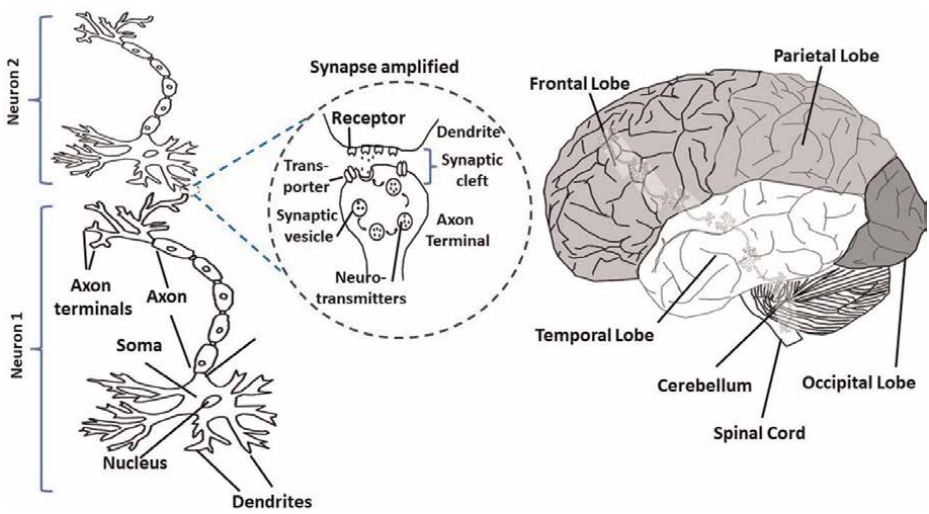
Figure 2.
(a) Two neurons connected, (b) "synaptic clef" amplified showing the chemical synapse process, and (c) the four human brain lobes, cerebellum and spinal cord.

4.2 The endocrine and stress hormone systems

The "endocrine system" is in charge of continuously monitoring and regulating all processes in the human body through hormones that are secreted into the blood stream by glands. The main glands are the "pineal gland, adrenal gland, pituitary gland, pancreas, ovaries, testes, thyroid gland, hypothalamus, and adrenal glands" [12]. The "endocrine system" provides a more generalized regulation by secreting hormones into the systemic circulation in the path of circulation between the heart and the rest of the body. The "ANS" and "endocrine system" have a high level of integration in the brain, with the ability to influence processes in distant regions of the body and maintain the tendency toward a relatively stable equilibrium between interdependent elements in physiological processes identified as "homeostasis". Using both systems as "chemical messengers" for the transmission of information from cells Several glands that signal each other in sequence are usually referred to as an axis. The most important for "stress" and "anxiety" is definitely the "hypothalamic-pituitary-adrenal axis." The "stress hormone system" is identified in the "hypothalamic-pituitary-adrenal axis (HPA axis)" that stimulates the "pituitary gland" to secrete 'adrenocorticotropic hormone (ACTH)" and stimulates the "adrenal cortex" to release "glucocorticoids" to function to maintain "physiological homeostasis".

> The "HPA axis*" is a major component in the "stress" response that allows physiological adaptation to the stressor to maintain "homeostasis".
> Note*: To be explained in sections 4.5, "HPA axis loops," and 4.6, "the theory for anxiety disorder: details overview."

4.3 Endocrine systems glands that release stress hormones

The "endocrine system" is responsible for regulating a range of bodily functions through the release of hormones. In this research, we focus on how it is activated when a stressful situation happens and produces hormones secreted by "glands" to handle "stress" and, by consequence, anxiety (as shown in **Figure 3**) to respond to the altered situation. These are identified as "stress hormones" and mainly they are "cortisol", "adrenaline", "norepinephrine", and "glucocorticoids".

- "Cortisol," a "glucocorticoid steroid hormone" from the "adrenal glands" located on top of each kidney as shown in **Figure 3**, produces hormones that regulate metabolism, immune system, blood pressure, response to stress, and development of sexual characteristics, among others. It is an "endocrine chemical messenger" that suppresses inflammation in all bodily tissues and controls metabolism in muscles, fat, the liver, and bones, besides affecting the "sleep-wake cycles" [13].

> "The body produces "cortisol" every day, according to a daily rhythm where our levels begin to rise in the last hours of sleep. They reach their peak levels about 30 to 40 minutes after we wake up. Then, they decrease until they are almost nothing unless a stressful situation is present.

- "Adrenaline" and "norepinephrine" are hormones from the "adrenal medulla," as shown in **Figure 3**. Where: Norepinephrine," also identified as noradrenaline," is
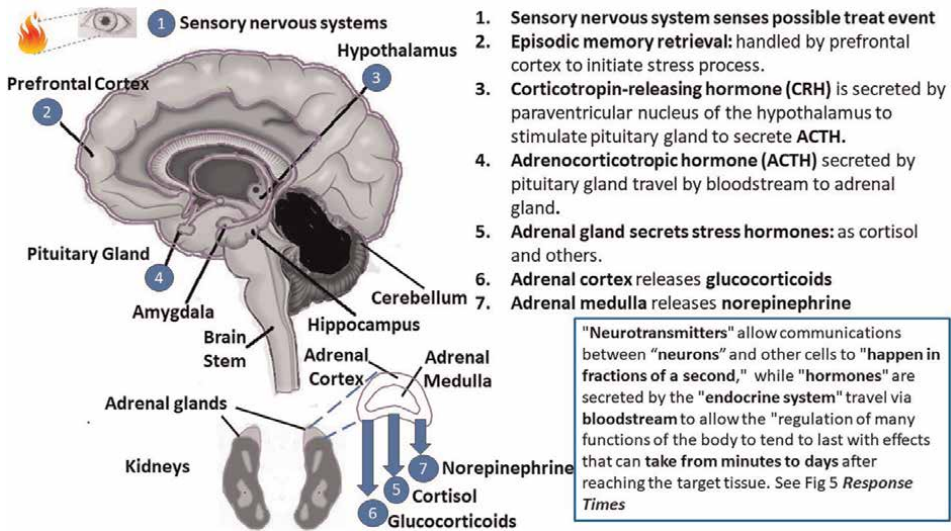
Figure 3.
Steps in the theory of anxiety disorder: Details and overview.

a "hormone" released by the "adrenal glands," and it is also a "neurotransmitter chemical messenger" that helps transmit nerve signals across nerve cells, muscle cells, or gland cells. "Norepinephrine" travels directly and indirectly to the brain, influencing learning and memory processes, and is involved in the initiation and maintenance of "fear" and "anxiety", modulating "episodic memory", fear conditioning, and fear reconsolidation [14]. "Adrenaline", also known as "epinephrine," is a hormone produced by the "adrenal medulla" inside the "adrenal glands". Its main function is to aid in the regulation of the sympathetic branch of the "autonomic nervous system".

> "Adrenaline" and "norepinephrine" are hormones that rapidly increase in the nervous system and metabolic system activity during "stress."

- "Glucocorticoids (glucose + cortex + steroid)" are "steroid hormones" that are secreted by the "adrenal glands" as anti-inflammatory and immunosuppressive actions that regulate "glucose metabolism" as a part of the "immune system" feedback to reduce inflammation [15].

4.4 Neurotransmitters involve handling stress and anxiety

Each of the two "brain hemispheres" has four sections identified as lobes, as shown in **Figure 2c**; these are: frontal, parietal, temporal, and occipital.

- The "frontal lobe" in the front of the head is involved in personality characteristics, decision making, movement, small recognition, and speech ability.

- The "parietal lobe" is in the middle of the brain and is involved in identifying objects and understanding spatial relationships, besides interpreting pain, touch, and helping the brain to understand spoken languages.

- The "occipital lobe" is on the back of the brain, and it is the place where vision is processed.

- The "temporal lobe" is on both sides of the brain, and many processes are executed for important functions, including short-term memory, speech, musical rhythm, and the smell recognition subprocess.

Deep in the brain, there are structures and glands that regulate "hormones" including the "pituitary gland", "hypothalamus", "hippocampus", "amygdala", and "pineal gland", as shown in **Figure 3**. Each brain organ function can be described as follows:

- The "pituitary gland" acts as a "master gland" controlling the function of other glands in the body and regulating the flow of hormones that are secreted on the "thyroid", "adrenals", and others. The "pituitary gland" is located just below the "hypothalamus" and connected to it through blood vessels and nerves identified as the "pituitary stalk", which is used for communication between the hypothalamus and the "anterior pituitary lobe" as bloodstream hormones and the "posterior lobe" through nerve as a neuronal connection [16], as shown in **Figure 3**.

> The pituitary gland secretes "(ACTH)" to stimulate the "adrenal cortex" part of the "endocrine system" to secrete glucocorticoids.

- "Hypothalamus" controls the "pituitary gland" sending "chemical messages" that control its function. Bedsides, plays a role in some aspects of memory and attention and regulates body temperature, synchronize sleep patterns, it also controls hunger and thirst.

> "Corticotropin-releasing hormone (CRH)" is secreted by the "paraventricular nucleus" in the hypothalamus as a response to stress, and it is identified as a central driver of the "stress hormone system," as shown in **Figure 3**.

- The "hippocampus," is an elongated ridge on the floor of each lateral ventricle of the brain hemispheres, is part of the "limbic system," as shown in **Figure 3**. It plays important roles in the consolidation of information in memory, including "short-term", "long-term", and "spatial" [17].

> The "hippocampus" is considered the center of emotion, memory, learning, navigation, perception of space, and the autonomic nervous system.

Note*: "Limbic systems" are structures and interacting areas involved in motivation, emotion, and memory. Besides, it is an important element in the body's response to "stress."

- "Amygdala" is part of the "limbic system" that regulates emotion and memory and is associated with the "reward system", "stress," and the responses when someone perceives a threat.

- "Pineal gland" is indicated in **Figure 3**. It helps in the regulation of female hormone levels, contributing to cardiovascular health and mood stability. It responds to light and darkness to secrete melatonin, which regulates "circadian rhythms" and the sleep-wake system [13]. "Circadian rhythms" are physical, mental, and behavioral changes that follow a 24-hour cycle. The "pineal gland" releases melatonin during the darkness of the night and decreases its production during daylight.

- "Cerebral Cortex" or "gray matter" is the brain's outermost layer of nerve cell tissue, consisting of nerve cell bodies, including the end portion of nerves called "dendrites," as shown in **Figure 2a**. They are the part of a nerve cell that receives the chemical message from another nerve cell. It plays a key role in memory, thinking, learning, reasoning, consciousness, emotions, and functions related to the senses.

The relationship of the "amygdala" to the "hippocampus" and "prefrontal cortex" is rich in "glucocorticoid" receptors and highly sensitive to stress, making them a very important circuit for fear conditioning [18].

"Anxiety" is frequently associated in many previous research papers with "sleep and circadian rhythms alterations" [19].

There is evidence that the "prefrontal cortex" has a critical function in executive functions that monitor and manage "episodic memory," as shown in **Figure 3**. These are "subjective experiences" captured to be remembered with details of past events that are triggered by present anxiety situations [20].

4.5 HPA axis loops

The "hypothalamic-pituitary-adrenal axis (HPA axis)" is a major component in the "stress" response that allows physiological adaptation to the stressor to maintain "homeostasis." This axis has three organs that interact to control reactions to handle "stress" and regulate many body processes such as digestion, immune responses, mood, emotions, sexual activity, and energy storage and expenditure with direct influences and feedbacks to maintain relatively stable equilibrium between them. These are the "hypothalamus", "pituitary gland" and "adrenal glands". The "HPA axis

"is a neuroendocrine pathway and feedback loop for many purposes; but it is mainly a "stress hormone system central driver" that stimulates the "pituitary gland" in the deep brain to secrete "adrenocorticotropic hormone (ACTH)" and stimulates the "adrenal cortex" to release "glucocorticoids" [21].

Understanding how the "HPA axis" works is essential to understanding how "stress" is handled by orders and feedback, which are explained in the next section.

4.6 The theory for anxiety disorder-details overview

The general overview of the "theory for anxiety disorders" is shown in **Figure 1**. In this section with details, we will overview the integration of the "HPA axis loops", visualize their integration with the "theory for anxiety disorders," as shown in **Figure 3**, and explain it in the following steps:

1. "The sensory nervous system senses external possible threat events." The "sensory nervous system," as a part of the nervous system, is responsible for processing external sensory information by sensory receptor neurons in vision, hearing, touch, taste, smell, and even internal visceral sensations as movements, inflammation, and pain from internal body organs alter, including heart palpitations, stomach inflammation, intestine cramps, kidney pain, and other unpleasant sensations [22].

2. "Episodic memory retrieval" is the concept of a memory system from our own experiences, including temporally dated information and spatiotemporal relations, that allows the re-experience of specific previous experiences with the possibility of being repeated for actual sensed events. "Episodic memory retrieval" is the interaction of many brain regions, including the temporal, parietal, and frontal cortices, mainly handled by the "prefrontal cortex", diencephalon as part of the forebrain, and cerebellum [23].

3. "Corticotropin-releasing hormone (CRH)". When the treat event detected is related to past experiences retrieved, the "CRH" is secreted by the "hypothalamus". It is the body's direct response to many forms of "stress", including physical and emotional stresses and internal and external stresses. Specifically, it is released by the "paraventricular nucleus" of the "hypothalamus" with the purpose of stimulating the "pituitary gland" as a part of the "HPA axis".

   Note*: An exaggerated increase in "CRH" production has been observed to be associated with Alzheimer's disease and depression [24].

4. "Adrenocorticotropic hormone (ACTH)" is secreted by the "pituitary gland" stimulated by "CRH" from the "hypothalamus", and travels via the "bloodstream" to both "adrenal glands" that are at the top of each kidney.

5. "Adrenal glands secrete a special kind of hormone identified as stress hormones". When the "adrenal glands" in the top of each kidney are stimulated by "ACHT"

they secrete hormones such as "cortisol", "glucocorticoids", "epinephrine," and "norepinephrine". "Cortisol" known as the "stress hormone", has many functions, including regulating stress response and metabolism, maintaining blood pressure, increasing, and regulating blood sugar levels, limiting inflammation*, and helping control the "sleep-wake cycle." "Cortisol is sent via the bloodstream" as a response to "stress".

The "sensory system" is in charge of detecting and processing information that is sensed in different places from the exterior senses and the interior as visceral sensation. It consists of sensory neurons, neural pathways, and brain parts involved in their processing.

Episodic memory retrieval is an internal process that finds, identifies, and mentally reconstructs past experiences related to learned lessons and compares them with the actual situation to determine the degree of the actual danger.

The "hypothalamus" makes many more hormones to communicate with and stimulate your pituitary gland: corticotrophin-releasing hormone (CRH), dopamine, gonadotrophin-releasing hormone (GnRH), and others.

ACTH is a hormone secreted as the body responds to "stress". It stimulates the "adrenal glands" to produce different hormones with the purpose of balancing the situation that generated the actual event of "stress".

Notes*: High levels of "cortisol" in the blood can lead to inflammation in a weakened immune system [25].

"The adrenal medulla secretes catecholamines; they are "hormones" that also function as "neurotransmitters". They are produced in the brain, nerve tissues, and "adrenal glands". The "adrenal medulla" secretes "catecholamines" to help the body respond to "stress". The main types of catecholamines include "norepinephrine" and "epinephrine". The main differences between them are summarized in **Figure 4**.

- "Norepinephrine," also known as "noradrenaline," is a part of the "HPA axis loop back" and plays an important role in the body's "acute stress" and when stress situations are repetitive, as in "chronic stress," with responses increasing alertness, arousal, attention, and focus, besides "constricting blood vessels to help maintain blood pressure when stress is present" and other functions such as increasing blood sugar levels.

- "Epinephrine" also known as "adrenaline" is secreted by the "adrenal medulla" in response to low blood sugar levels or exercise, helping the body to deliver extra oxygen to muscles, increase blood pressure and heart output, and "widen small

Epinephrine and Norepinephrine general behavior

- As "Hormones" travel through bloodstream to reach and turn on signals responsible for regulating the physiological changes by the body in response to stress or fear
- As "Neurotransmitter" are chemical messengers sending signals between nerve cells to activate autonomic nervous system responsible for controlling certain systems in the body, such as heart rate, breathing, and digestion.
- When the brain feels a sense of danger, the autonomic nervous system tells the adrenal gland to release epinephrine into the bloodstream.

Epinephrine (adrenaline) effects	**Norepinephrine (noradrenaline) effects**
When released, body feels adrenaline rush to boost organ functioning: • increasing heart rate • fast breathing • elevated blood sugar levels • increased physical strength • pain perception is reduced	It is always present in our blood in small amounts during stressful situations: • adrenal medulla releases more to help maintain • blood pressure narrowing blood vessels • increasing blood sugar levels

Note 1: "**Cortisol**" is a glucocorticoid a type of steroid hormone for regulate stress that your adrenal glands produce and release. It suppress inflammation in all bodily tissues and control metabolism in your muscles, fat, liver and bones

Note 2: "**Dopamine**" is another main type of catecholamine; it is a neurotransmitter that sends signals throughout the nervous system. It helps regulate the following: movement, emotions, memory, and it is a brain's reward mechanism

Figure 4.
Differences between "norepinephrine" and "epinephrine". Besides, two special comments about "cortisol" and "dopamine".

arteries". It has two roles as a "hormone" that is released by the "adrenal glands" in response to "stress" but is also a "neurotransmitter" that participates in the "synapses" cells as shown in **Figure 2** as a part of the "sympathetic nervous system", Its reaction causes many changes in the body during stressful events commonly known as the "fight-or-flight response"; this is a response to stay and fight the dangerous event or run to safety. These reactions occur when the brain perceives danger, nerves in the "hypothalamus" send a signal down to the "spinal cord and then to all body organs and tissues": pupils are dilated in the eyes, skin turns pale because blood vessels divert blood that needs more oxygen as muscles fight or run away, the heart pumps harder to deliver more oxygenated blood to muscles for more strength, glycogen is stored in the liver to be ready to be converted to glucose, breathing is deeper and faster for more oxygen in the muscles, etc. These reactions continue until the brain senses that it is out of danger.

- The "adrenal cortex" secretes "glucocorticoids" as a part of the "HPA axis loop back", these are "natural steroids" with many functions as interrupt inflammation by moving into cells and suppressing the proteins that promote inflammation.

"Dopamine" is another main type of catecholamine; it is a neurotransmitter that sends fast signals throughout the nervous system. It helps regulate the following: movement, emotions, and memory, and it is the brain's reward mechanism.

"Glucocorticoids (GCs = glucose + cortex + steroid)" are "steroid hormones," and they are essential for the termination of the stress response.

4.7 Summarizing main differences between hormones and neurotransmitters

The human body to function properly needs "hormones" and "neurotransmitters", both are chemical messenger as explained on Section 4.3 and 4.4, the main differences between them are summarized on **Table 1**.

The steps for the "Theory for Anxiety Disorder: Details Overview" can be visualized in the estimated time each "neurotransmitter chemical messenger" and "endocrine chemical messenger" takes to reach their receptor, as shown in the chain reaction sequence response in **Figure 5**.

5. Conclusions

Integrating the information shown in **Figures 1** and **2**, it is noticeable that the interaction of the 'HPA axis" with neuroendocrine pathways and the feedbacks has different travel times; some are through the "autonomic nervous system" and others through the "bloodstream" as the blood circulates through the body. Both are necessary, but the event response time between them seems to overlap when "anguish" and "anxiety" events are constantly triggered, as shown in **Figure 3** and when visualizing the event time response in **Figure 5**.

The most important issue result of this research for "anxiety disorder" is: "Neurotransmitters" allow communications between neurons and other cells to

Characteristic	Hormones	Neurotransmitters
Molecules	Are mainly peptides, amines, terpenes* or steroids. * Terpenes are bioactive compounds that are easily absorbed and accepted by the body and aid in balancing the production of crucial neurotransmitters like serotonin and dopamine. They have a positive impact on our mood	Less varied: usually peptide molecules, amino acids, or gases
Transmission mode	via the bloodstream to affect other tissues	Strict "synaptic" method of communication between cells.
Function Range	"Long-range": organs or tissues that target hormones are sent a distance by the bloodstream	"Limited range" only affects cells that are connected through synaptic junction
Tissues range	Usually multi-targeted, various organs/tissues	Only in adjacent cells, mostly in the same tissue, with the exception of neuromuscular synapse
Response time	Tend to last, with effects that can take from minutes to days after reaching the target tissue.	Fractions of a second.
Effects modulation	The purpose of stabilizing blood levels, fluctuation, inhibiting or promoting the release of hormones to other tissues, and receptor availability	Neurotransmitters that are transmitted in the synapse, produce effect that depends on the affected cell type and are "all or nothing", depending on whether or not the next cell is activated.

Table 1.
Main differences between hormones and neurotransmitters.
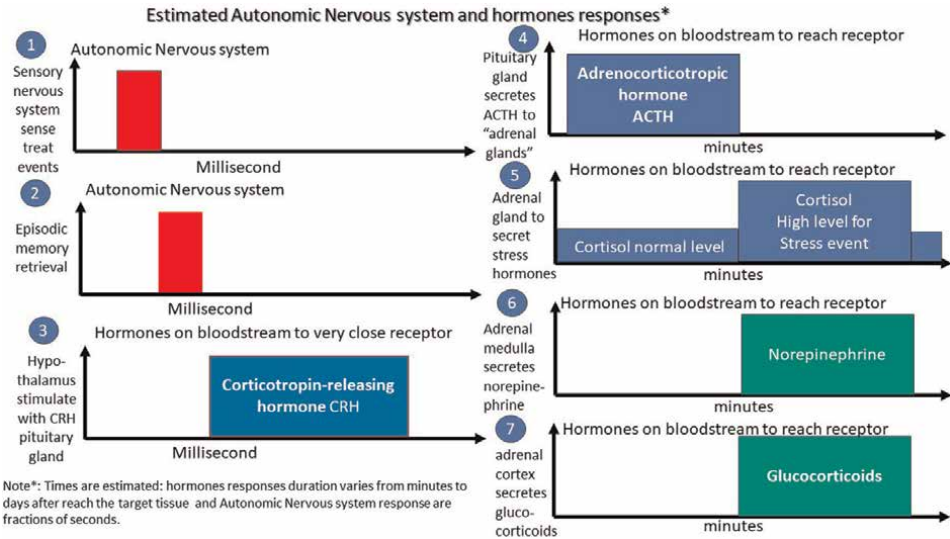
Figure 5.
Estimated autonomic nervous system and endocrinology system hormone response times for the "Theory for Anxiety Disorder: Details Overview".

"happen in fractions of a second," represented in milliseconds in **Figure 5**, while "hormones" are secreted by the "endocrine system" travel via bloodstream to allow the regulation of many functions of the body to tend to last with effects that can take from minutes to days after reaching the target tissue, represented in minutes in **Figure 5**.

Summarizing the "theory for anxiety disorder" exposed in this research, there are at least three concepts that deserve immediate attention:

- Frequency of stress situations.

- Failure to react to avoid repeated exposure to stress situations, and

- Finding ways to handle and turn off unnecessary responses to false threats.

All three affect the increased risk for the development of an "anxiety disorder", and as far as is known, they can be treated with "cognitive behavioral therapy (CBT)". CBT focuses on teaching the anxiety patient to develop specific skills to improve the symptoms and return to normal activities step by step. But it is also possible to develop cognitive computing applications to help with this kind of treatments, as explained in my book "Applied Biomedical Engineering Using Artificial Intelligence and Cognitive Models" [26].

Some commons reasons that trigger "anxiety" continuously are:

- "Hard times for humanity" are confronting a huge number of continuous disasters.

- "Climate change" is affecting our environment.

- "Bacteria and viruses" of different kinds that have been evolving as a treat for pandemic times,

- "Economic daily impacts" in our expenses compared with the cost of living incremented continuously to cover the cost of the basic needs such as healthy food, clean water, clean air quality, and the inevitable need to sleep well.

- "Smart devices with artificial intelligence" technological advances that are programed to take continuous attention, making frequent changes in our way of living, widen the amount of information that we receive and process on a daily basis [27].

- Genetics reasons, and many others.

6. Recommendation

> **"In order for something to be improved,**
> **It must be understood and measured."**
> There is an urgent need to develop methods to evaluate "anxiety" and "anxiety disorder" with objective mode methods that measure real values, beside the actual "subjective mode". I will allow me to mention some of the many research papers doing this that I hope to have the opportunity to document and analyze in a future book chapter.

Some research has found "measuring hair cortisol concentration ranges by automated methods", "associations between chronic stress and hair cortisol concentration" and "evaluation of chronic stress on the hypothalamic-pituitary-adrenal (HPA) axis":

- "Measuring hair cortisol concentration ranges by automated methods [28]", they found that hair cortisol concentration median measurements by an automated method are:

  - For a healthy individual with low levels of stress, 55 picograms per milligram of hair (pg/mg) with a 2.5–97.5 percentile (40–128),

  - For stressed individuals is 250 pg./mg of hair (range 182–520).

- "Associations between chronic stress and hair cortisol concentration (HCC)" when stressful life events within the past 6 months show a congruent time of stress with HCC stronger pooled correlation in thirteen studies from five countries with 1455 participants [29].

- "Evaluation of chronic stress on the hypothalamic-pituitary-adrenal (HPA) axis [30]." "Cortisol" is a recommended hormone for evaluation of "chronic hyperactivity" of the "hypothalamic-pituitary-adrenal (HPA) axis" in situations of "chronic stress".

These cortisol ranges values can be used as a reference for other cortisol research papers and labs tests.

This research confirms the relation between chronic stress and cortisol, deducted in the theory for anxiety disorders in this chapter.

They found that cortisol variability during the circadian rhythm can be measured in the growing hair follicle that is incorporated into hair sections as it grows; they also claim that 3 cm of hair would reflect the cortisol levels of a patient in the last 3 months.

Thanks to all previous research that apportioned invaluable information and results with their research work on "anxiety" and "anxiety disorders".

Notices: Knowledge and best practice in this field are constantly changing as new research and experience broaden our understanding, and changes in research methods, professional practices, or medical treatment may become necessary. To the fullest extent of the law, neither the publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence, or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein [31].

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Chapter 4

Anxiety and Anguish: Navigating Psychological Corridors from Childhood to Adulthood

Ramasubbareddy Challa and Swetha Alahari

Abstract

This work delves into the intricate journey of individuals as they grapple with anxiety and anguish throughout the pivotal transition from childhood to adulthood. Drawing from extensive research and clinical insights, this chapter comprehensively explores the multifaceted factors contributing to these complex emotional states' development, manifestation, and management. It serves as a foundational exploration of the intricate dynamics that shape anxiety during childhood, setting the stage for a comprehensive understanding of emotional development throughout the lifespan. The chapter delves into the origins of childhood anxiety and anguish, shedding light on the formative experiences, familial dynamics, and societal influences that shape emotional well-being during early developmental stages. As the narrative progresses into adolescence and young adulthood, readers gain a deeper understanding of how anxiety and anguish can evolve, intensify, or manifest in various forms, including generalized anxiety disorder, social anxiety, and panic disorders. Crucially, "Anxiety and Anguish" also delves into evidence-based strategies and therapeutic approaches for managing and alleviating these emotional challenges. The chapter emphasizes the importance of early intervention and holistic support systems in promoting resilience and well-being throughout the transitional phase. With its blend of scientific rigor and practical insights, "Anxiety and Anguish: Navigating Psychological Corridors from Childhood to Adulthood" is an indispensable resource for clinicians, educators, parents, and anyone seeking a deeper comprehension of the intricate emotional terrain traversed by individuals as they navigate the challenging journey from childhood to adulthood. This work not only elucidates the complexities of anxiety and anguish but also offers hope and guidance for individuals and communities striving to foster emotional well-being during this critical life stage.

Keywords: anxiety, anguish, emotional, childhood, adulthood

1. Introduction

In the vast tapestry of human emotions that exists, feelings oscillate between fleeting moments of unease and profound states of distress. Anchoring this spectrum are two sentiments deeply familiar to many: anxiety and anguish. Though sometimes used interchangeably in casual conversation, each embodies a unique facet of emotional

experience. Their grasp on our psyche, motivations, and daily lives can be profound. In this chapter, we aim to unpack the intricacies of anxiety and anguish, charting their origins, manifestations, and the indelible mark they leave on the human experience.

Anxiety: At its core, anxiety is a future-oriented state of mind. It emerges from our brain's ability to anticipate, imagine, and worry about what's yet to come. This evolutionary tool, beneficial in moderation, can become paralyzing when taken to the extreme. Whether it's the jittery feeling before a big presentation or the relentless dread that some face daily, anxiety's footprint is diverse, affecting each individual differently.

Anguish: Rooted in the present and colored by the past, anguish dives deep into the realm of current suffering and distress. Often born from loss, trauma, or profound existential reflections, anguish is not merely an emotion—it's a state of being. It speaks to our deeper vulnerabilities, echoing pain, despair, and, sometimes, a yearning for meaning.

The journey ahead will lead us through these emotions' psychological alleyways and biological underpinnings, their impact on our behaviors, and the therapeutic avenues available. By understanding anxiety and anguish, we embark on a path of comprehension, empathy, self-awareness, and healing. Welcome to exploring two of the most compelling emotions in the human repertoire.

The terms "anxiety" and "anguish" are often used interchangeably, but they refer to slightly different emotional states. Both can have significant impacts on an individual's mental, emotional, and even physical well-being. Let us delve into their distinctions and the anxiogenic (anxiety-producing) effects they can have.

1.1 Definitions

- *Anxiety*: This is a feeling of unease, such as worry or fear, that can be mild or severe. It often relates to something that is perceived as a potential future threat. Anxiety disorders include generalized anxiety disorder, panic disorder, social anxiety disorder, and specific phobias, among others.

- *Anguish*: This term is more general and can refer to severe mental or emotional pain or distress. It can result from trauma, loss, or other significant dynamic events. Anguish is deeper than typical anxiety and tends to be more existential or philosophical.

2. Philosophical and relational studies

Philosophy and human relations offer profound insights into the nature and experience of anxiety and anguish. Such introspections shed light on individual experiences and the collective consciousness of societies and civilisations. This chapter will explore the philosophical interpretations and the intricacies of human relationships surrounding these emotions.

2.1 Philosophical interpretations

2.1.1 Søren Kierkegaard

Often dubbed the "father of existentialism," Kierkegaard viewed anxiety as a result of human freedom and possibility [1]. For him, the angst one feels when confronted with infinite possibilities encapsulates the existential condition.

2.1.2 Existentialism and the human condition

2.1.2.1 Existential anxiety (Angst)

Heidegger introduced the concept of "Existential Anxiety" or "Angst" as a fundamental aspect of human existence. Unlike ordinary anxiety, which is usually triggered by specific external events, existential anxiety is a pervasive and profound feeling of unease that arises from our confrontation with the ultimate questions of existence [2].

2.1.2.2 Finitude and mortality

Heidegger argued that anxiety emerges from our awareness of our own mortality and the finite nature of human existence. We grapple with the fact that our time on Earth is limited, and this awareness generates a sense of dread and unease.

2.1.2.3 Being-towards-Death (Sein zum Tode)

Heidegger believed that authentic existence involves confronting our mortality head-on. He introduced the concept of "Being towards death," which means recognizing that death is an inevitable part of life and using this awareness to make meaningful choices. Instead of denying or avoiding death, we should embrace it as an essential aspect of our existence.

2.1.2.4 Alienation and everydayness

Heidegger also discussed how, in our everyday lives, we often fall into a state of "das Man" (the "They" or the "One"), where we conform to societal norms and expectations, leading to a sense of alienation from our authentic selves. Anxiety can arise when we confront the inauthenticity of our existence in these moments.

2.1.2.5 Freedom and authenticity

Heidegger believed that confronting anxiety can lead to a sense of freedom. By acknowledging our anxieties and embracing our authentic selves, we have the potential to make more meaningful and autonomous choices, leading to a deeper sense of fulfillment and purpose.

- *Jean-Paul Sartre*: Sartre believed that anguish arises from the human realization of their inherent freedom, leading to the overwhelming responsibility for their actions [3].

2.1.3 Phenomenology and embodied emotion

1. *Phenomenological approach to anxiety and anguish:* Phenomenological psychology aims to understand human experiences from a first-person perspective, emphasizing psychological phenomena' subjective and lived aspects. When it comes to anxiety and anguish, phenomenological psychologists explore how individuals experience and make sense of these emotions in their everyday lives [3, 4].

2. *Phenomenological reduction:* Phenomenological reduction is a key method used in this approach. It involves suspending preconceived notions and judgments to grasp the essence of a phenomenon. When applied to anxiety and anguish, it helps researchers uncover the fundamental characteristics of these emotions as they are experienced by individuals, free from external interpretations or assumptions.

3. *Temporal structure*: Phenomenological investigations often reveal that anxiety and anguish are intertwined with the temporal structure of human existence. Anxiety can be linked to future-oriented concerns and possibilities, while anguish often involves a sense of despair or dread concerning one's past or future.

4. *Martin Heidegger:* In phenomenological psychology, Martin Heidegger's work, particularly his concept of existential anxiety (Angst) as discussed in "Being and Time," is a foundational reference. Heidegger's insights into the nature of anxiety and how it relates to one's being in the world have influenced phenomenological psychologists' exploration of these emotions [2].

5. *Maurice Merleau-Ponty:* From a phenomenological perspective, Merleau-Ponty emphasized the embodied nature of human experience. Anxiety and anguish are not just mental states but are deeply intertwined with our physical being.

2.1.4 Eastern philosophies

- *Buddhism*: Suffering (dukkha) is one of the Four Noble Truths. Anxiety and anguish can be seen as forms of suffering arising from attachment and alleviated through mindfulness, understanding, and the Eightfold Path.

2.2 Relational dynamics

2.2.1 Attachment theory

- *John Bowlby:* Bowlby's work on attachment suggests that early relationships shape our emotional responses, especially with primary caregivers. Individuals with insecure attachments may experience heightened anxiety in relationships [5].

2.2.2 Interpersonal relationships and social structures

- *Social anxiety:* Rooted in the fear of negative evaluation in social settings, this form of anxiety can be understood as a result of complex relational dynamics.

- *Collective anguish*: Large-scale traumas, such as wars or natural disasters, can lead to collective feelings of anguish, impacting the relational fabric of entire communities or nations.

2.2.3 The role of modern communication

- *Digital age distress*: The rise of social media and instant communication has influenced our relational dynamics. The constant comparison, the need for validation, and the immediacy of interactions can amplify feelings of anxiety and anguish.

3. Anxiety and anguish: From childhood to adulthood

3.1 From childhood to adulthood

Anxiety and anguish are two intertwined emotional states that can pervade one's life from the earliest memories to the final days. In understanding their progression and impact across various life stages, we can better equip ourselves to cope, understand, and potentially alleviate these emotions [6, 7].

Anxiety and anguish in children is a topic of deep concern, as these emotions can significantly impact a child's well-being, development, and overall life experience. Recognizing, understanding, and addressing these feelings is crucial for parents, educators, and mental health professionals.

From the cradle to the twilight years, anxiety and anguish can shape our experiences. Recognizing, understanding, and addressing these emotions at every stage can lead to a more fulfilling and balanced life. As we progress through life's journey, it's essential to remember that these feelings are a universal part of the human experience, and there's always hope and help available.

3.2 Causes

1. *Developmental transitions:* Normal developmental stages can sometimes trigger anxiety. For instance, starting school or moving to a new grade can be anxiety-provoking for some children.

2. *Traumatic events*: Accidents, deaths in the family, witnessing violence, or being a victim of abuse can cause significant anguish and anxiety.

3. *Environmental factors*: Family dynamics, parental stress, bullying, or academic pressures can contribute to anxiety and anguish.

4. *Physical health:* Medical conditions or medications sometimes cause or exacerbate anxiety.

5. Genetics: Some children might be genetically predisposed to anxiety due to their family history.

6. Childhood: The foundation [8, 9]

   - *Infancy and early development:* Anxiety is not limited to verbal expression. Infants, for instance, may experience anxiety during separations from caregivers (separation anxiety). They pick up on environmental cues, with a hypersensitivity to the emotional states of those around them.

   - *Toddler years*: As toddlers begin to explore the world, stranger anxiety develops. They become wary of unknown faces. This is a normal part of development rooted in our evolutionary past.

   - *School age*: Starting school is a significant milestone. Children now face social anxieties, performance anxieties, and fear of failure.

Friendships, peer acceptance, and academic expectations become dominant aspects of their lives.

7. Adolescence: The crucible of change [8, 9]

   - *Physical changes:* Puberty brings with it a plethora of hormonal changes. This, coupled with the inevitable physical changes, can amplify feelings of self-consciousness and anxiety about one's appearance and acceptance.

   - *Identity and existential anguish:* Teens grapple with identity, purpose, and the future. Questions about "Who am I?" and "What is my purpose?" can generate significant anguish.

   - *Social and peer pressures:* The need for acceptance peaks. Social anxieties may develop or intensify due to the fear of exclusion, bullying, or the challenges of navigating first romantic relationships.

8. Early adulthood: Seeking stability

   - *Career and performance anxiety:* Early adults often feel the pressure to solidify their place in the world. Career choices, job performance, and financial independence can be sources of significant stress and anxiety.

   - *Relationship and familial pressures:* As individuals form long-term partnerships or start families, anxieties related to being a good partner or parent emerge. The balance between personal aspirations and family responsibilities can cause anguish.

9. Middle adulthood: Midlife reflections

   - *Existential crises*: Often termed the "midlife crisis," individuals may begin to reflect deeply on the life they have lived and what lies ahead. This can result in feelings of regret, unfulfillment, or fear of mortality.

   - *Parenting anxieties:* As children grow and face their challenges, parents might experience anxiety about their kids' futures, choices, and well-being.

10. Late adulthood: Coming to terms

   - *Health anxieties:* As the body ages, concerns about health, physical capabilities, and mortality become more pronounced.

   - *Legacy worries:* Late adults often think about what they are leaving behind, be it in terms of financial inheritance, moral teachings, or just memories.

3.3 Symptoms

1. *Physical symptoms*: Stomachaches, headaches, difficulty sleeping, or fatigue.

2. *Behavioral symptoms*: Avoidance of certain activities or places, clinging behavior, irritability, or throwing tantrums.

3. *Emotional symptoms*: Constant worry, negative thoughts, feelings of hopelessness, or crying without obvious reasons.

4. *Cognitive symptoms*: Difficulty concentrating, forgetfulness, or decline in academic performance.

3.4 Management and support

1. *Open communication*: Encourage the child to talk about their feelings. Listening without judgment and offering reassurance can be therapeutic [10–13].

2. *Professional support*: Therapy, especially cognitive-behavioral therapy (CBT), has proven beneficial for many children suffering from anxiety. In more severe cases, medication might be recommended.

3. *Routine*: A consistent routine can offer a sense of normality and predictability.

4. *Healthy lifestyle*: Ensure the child gets enough sleep, follows a balanced diet, and engages in regular physical activity.

5. *Limiting stress*: If possible, identify stressors and find ways to reduce or eliminate them.

6. *Education*: Teaching children about anxiety can help them better understand and manage their feelings. There are many age-appropriate books and resources available.

7. *Parental self-care*: Parents should also care for their own mental health, as children often mirror the emotions of those around them.

If you suspect a child is suffering from intense anxiety or anguish, it's essential to seek professional help. Early intervention can make a significant difference in a child's life.

3.5 Interventions and coping

Across all life stages, there are common and stage-specific interventions [10–13]

1. *Therapy*: Cognitive-behavioral therapy, for instance, can provide coping tools and strategies.

2. *Medication*: In cases where anxiety is severe, pharmacological interventions might be recommended.

3. *Mindfulness and meditation*: Techniques that promote self-awareness can help individuals manage and reduce anxiety.

4. *Social support*: Building and maintaining strong social connections provides a buffer against anxiety and anguish.

4. Risk factors of anxiety and anguish

Anxiety disorders are the most prevalent mental health conditions. They can be evident in various forms, one of the most acute being panic attacks. A panic attack can be an intensely frightening experience, often described as a sudden surge of overwhelming fear or discomfort. These attacks can come on abruptly and peak within minutes [8, 10, 14].

Let us delve into the risk factors for anxiety disorders and then discuss the features of panic attacks:

4.1 Risk factors for anxiety disorders

1. *Genetics*: A family history of anxiety can increase one's risk.

2. *Brain chemistry*: Abnormalities or imbalances in certain neurotransmitters can be linked to anxiety.

3. *Personality*: Certain personality types may be more susceptible to anxiety disorders.

4. *Life events*: Traumatic or stressful events, such as abuse, the death of a loved one, divorce, or changing jobs/schools, can trigger anxiety or exacerbate it.

5. *Chronic medical illnesses*: Conditions like heart disease, diabetes, or asthma can increase the risk of developing an anxiety disorder.

6. *Substance abuse*: Excessive consumption of alcohol or drugs can induce anxiety symptoms. Moreover, withdrawal from certain drugs can lead to anxiety or panic.

7. *Gender*: Women are generally more prone to anxiety disorders than men.

4.2 Panic attacks

Panic attacks are characterized by a combination of physical and psychological symptoms that can be very intense and distressing. These can include:

1. *Rapid heartbeat*: This can make a person feel as if their heart is racing or pounding.

2. *Sweating*: Profuse sweating often accompanies a panic attack.

3. Trembling or Shaking

4. Shortness of Breath or a Feeling of Choking

5. Chest Pain or Discomfort

6. Nausea or Stomach Cramps

7. Dizziness or Light-headedness

8. Chills or Hot Flashes

9. Fear of Dying or Losing Control

10. Numbness or Tingling Sensations

11. Feelings of Unreality (Derealization) or Being Detached from Oneself (Depersonalization)

4.3 Anguish

Anguish often refers to extreme pain or distress, either physical or, more commonly, emotional. The emotional experience of anguish can be closely tied to anxiety and may manifest as feelings of desperation, extreme sadness, or hopelessness.

4.4 Management

If someone experiences recurrent panic attacks or chronic feelings of anxiety and anguish, seeking medical and psychological help is essential. Various treatments are available, including [8, 10, 11, 15–18]:

1. *Therapy*: Cognitive-behavioral therapy (CBT) is particularly effective in treating panic and generalized anxiety disorders.

2. *Medication*: Certain antidepressants, benzodiazepines, or beta-blockers can be prescribed to treat symptoms.

3. *Lifestyle changes*: Avoiding caffeine and alcohol, practising relaxation techniques, maintaining a regular sleep pattern, and engaging in regular exercise can help manage symptoms.

4. *Education*: Understanding anxiety can sometimes help people cope better.

5. *Support groups*: Talking with others who have similar experiences can be reassuring and provide mutual support.

In summary, while anxiety disorders and their associated panic attacks can be distressing, understanding their risk factors and symptoms can aid in seeking timely treatment and support.

5. Epidemiology of anxiety and anguish

Anxiety disorders are the most common mental health disorders worldwide affecting. Anxiety disorders are the most frequent type of mental health illness,

impacting an estimated 264 million people of all ages worldwide. Anguish is a strong form of anxiety marked by feelings of extreme anguish, fear, and despair [19].

Cultural variations can also influence how people seek care for their anxiety and pain. In some cultures, seeking professional care for mental health issues may be frowned upon. People in various cultures may seek help from traditional healers or religious leaders.

5.1 Examples of cultural differences in anxiety and anguish

- Anxiety is more likely to manifest physically in some Asian cultures, such as stomach problems or headaches. Anxiety may be exhibited more emotionally in some Western cultures, such as grief or rage.

- Traditional healers or religious leaders may be more likely to treat persons suffering from anxiety and misery in some societies. People in other cultures may be more likely to seek professional assistance from a mental health specialist.

- Seeking professional help for mental health concerns may be considered taboo in some cultures. There may be no such taboo in other civilizations.

It is crucial to emphasize that these are only broad generalizations, with significant individual diversity within each culture.

1. *Global prevalence*: Anxiety disorders are some of the most common mental disorders worldwide. The World Health Organization (WHO) has highlighted that globally, over 260 million people are affected by anxiety disorders.

2. *Lifetime prevalence*: In the U.S., the lifetime prevalence of any anxiety disorder is about 28.8%. This means that approximately 1 in 3 people will experience an anxiety disorder at some point in their life [19].

5.2 Risk factors

1. *Gender*: Women are approximately twice as likely as men to be diagnosed with certain anxiety disorders over their lifetime.

2. *Age*: Onset of anxiety disorders can occur in childhood, adolescence, or adulthood, though certain conditions like Separation Anxiety Disorder and Specific Phobias often begin in childhood.

3. *Socioeconomic status*: Individuals in lower socioeconomic groups might have a slightly higher risk for certain anxiety disorders due to increased exposure to stressors [20].

5.3 Comorbidity

1. Comorbid mental disorders: Anxiety disorders frequently co-occur with other mental health disorders, such as depression.

2. Physical health conditions: Individuals with anxiety disorders often have concurrent chronic physical conditions like cardiovascular disease or diabetes.

Outcomes:

1. Impairment: Anxiety disorders can significantly impair daily functioning, limit life opportunities, and decrease overall quality of life

   It's important to note that "anguish" is a term that can denote extreme pain or distress. While it may be used to describe feelings associated with anxiety disorders, it is not a technical term in the field of psychiatric epidemiology. However, the feelings of distress, worry, and unease common to anxiety disorders can evoke anguish in many individuals [20, 21].

The term "anguish" is not commonly used in modern psychiatric terminology in the same clinical sense as anxiety. However, it often refers to a profound feeling of severe pain, suffering, or distress, which might be part of or a result of anxiety disorders or other mental health conditions.

If you or someone you know is experiencing symptoms of anxiety or anguish, consulting a mental health professional is recommended for an accurate diagnosis and appropriate treatment [20–22].

6. Avoidance and separation anxiety disorder in anxiety and anguish

1. Avoidance: Avoidance behaviors can be found in various anxiety disorders. Individuals may go to great lengths to prevent encountering a situation or object that provokes fear or anxiety in them [14, 23].

6.1 Associated disorders

- *Generalized anxiety disorder (GAD)*: Individuals may avoid certain situations out of worry or fear.

- *Panic disorder*: People may avoid places or situations where they have had panic attacks before, fearing another occurrence.

- *Social anxiety disorder (SAD)*: There's a fear of social situations, leading individuals to avoid parties, meetings, or even small gatherings.

- *Specific phobias:* The avoidance is specific to a particular object or situation, such as heights, animals, or flying.

6.2 Manifestations

- Chronic avoidance can restrict one's life and lead to isolation.

- The individual may recognize the fear as irrational but feels powerless to change.

- Physical symptoms such as sweating, trembling, or rapid heart rate may accompany exposure to the feared situation or object.

2. Separation Anxiety Disorder (SAD): Separation anxiety disorder is not limited to children; it can also affect adults. It involves excessive fear or anxiety about separation from those to whom the individual is attached.

6.3 Characteristics

- Extreme distress when thinking about or experiencing separation from home or major attachment figures.

- Persistent reluctance or refusal to go to school or elsewhere because of fear of separation.

- Recurrent nightmares about separation.

- Physical complaints, like headaches or stomachaches, when separation is anticipated.

6.4 Etiology

1. SAD may be triggered by a traumatic event, such as the death of a loved one, or even less severe events like changing schools.

2. Overprotective or intrusive parenting can sometimes contribute to the development of SAD.

6.5 Manifestations

- May cling to their parent or other caregiver.

- They might avoid activities or events because of fear of separation.

- They can become socially isolated and have difficulty making friends or maintaining relationships.

Overall Anguish in Both Disorders: The anguish felt in both disorders is a product of the anxiety experienced. Anxiety often manifests as a physical sensation of unease, ranging from mild discomfort to severe panic. Over time, untreated anxiety disorders can affect various aspects of an individual's life, leading to problems in relationships, job performance, and physical health.

Treatment: Both types of disorders can benefit from cognitive-behavioral therapy (CBT), which aims to change patterns of thinking or behavior that contribute to a person's symptoms. Medications, including SSRIs, can also be effective.

In summary, both avoidance and separation anxiety disorder revolve around a central theme of anxiety and the anguish it brings. However, their causes, manifestations, and methods of coping can differ greatly. Recognizing and treating these disorders can help individuals lead more fulfilling, less restricted lives.

7. Measurement of anxiety

1. Self-report Scales:

    - State–trait anxiety inventory (STAI): One of the most widely used tools to assess anxiety. It measures both state anxiety (how a person feels at the moment) and trait anxiety (how a person generally feels) [24].

    - Beck anxiety inventory (BAI): This questionnaire assesses the severity of a person's anxiety.

    - Generalized anxiety disorder 7 (GAD-7): This short questionnaire identifies generalized anxiety disorders.

2. Physiological measures: Certain physiological changes can indicate anxiety, such as increased heart rate, elevated cortisol levels, and heightened skin conductance.

3. Clinical interviews: Structured interviews, such as the Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5), can be used by clinicians to diagnose anxiety disorders [22].

4. Observational methods: Behavioral observations in controlled settings can provide insights into anxiety reactions.

7.1 Measurement of anguish

1. Self-report Scales:

    - While there are no standard scales specifically for "anguish," various scales measure psychological distress, which can encompass feelings of anguish. These include the Kessler Psychological Distress Scale (K10) and the Brief Symptom Inventory (BSI).

2. Clinical interviews: Mental health professionals can assess feelings of anguish during structured or unstructured interviews, understanding the depth and causes of the suffering.

3. Narrative approaches: Allowing individuals to narrate their experiences can be an effective way of understanding anguish, especially if it arises from traumatic events.

4. Physiological measures: While physiological measures alone cannot pinpoint anguish, extreme distress can result in certain physiological responses, such as changes in heart rate variability or stress hormone levels [10].

It's essential to note that self-report measures, while valuable, rely on the individual's ability to introspect and report their feelings accurately. Combining self-report with other measures (e.g., physiological, observational) can offer a more comprehensive picture of the individual's emotional state.

Finally, context is crucial. Understanding the underlying causes or triggers for anxiety or anguish can provide valuable insights for intervention and support. If someone is experiencing these feelings, seeking professional help is crucial, as prolonged anxiety and anguish can lead to other mental health challenges.

8. Anxiogenic effects of anxiety and anguish

8.1 Anxiogenic effects

- *Physical symptoms*: Both anxiety and anguish can lead to physical symptoms such as palpitations, trembling, sweating, gastrointestinal issues, headaches, muscle tension, and insomnia. These symptoms can further exacerbate feelings of unease, creating a feedback loop [10, 13, 17, 21].

- *Cognitive distortions*: Anxiety can warp perceptions and thinking patterns, especially when chronic. This can lead to cognitive distortions like catastrophizing (expecting the worst), black-and-white thinking, and overgeneralization.

- *Avoidance behavior*: One of the hallmarks of anxiety is the tendency to avoid situations or stimuli that provoke anxious feelings. Over time, this can lead to isolation and a restriction in life activities.

- *Depression*: Extended periods of anxiety or anguish can lead to feelings of hopelessness and even depression. The weight of persistent worry or distress can sap energy and motivation.

- *Substance abuse*: Some individuals use alcohol, drugs, or other substances to cope with or escape their anxiety and anguish. This can lead to substance abuse or addiction.

- *Existential crisis*: Especially relevant for anguish, the profound emotional pain can lead to existential or philosophical crises, where individuals question the meaning and purpose of life.

8.2 Coping and treatment

Recognizing the impact of anxiety and anguish on one's well-being is the first step towards managing them. Effective coping strategies include:

- *Professional therapy*: Cognitive-behavioral therapy (CBT), exposure therapy, and other therapeutic approaches can help individuals address and manage their anxiety and anguish.

- *Medication*: Some people benefit from anti-anxiety medications or antidepressants.

- Mindfulness and meditation: Techniques that promote relaxation and present-moment awareness can reduce the intensity and frequency of anxious feelings.

- *Lifestyle changes*: Regular exercise, a balanced diet, adequate sleep, and avoiding caffeine and certain medications can help reduce anxiety.

In conclusion, while anxiety and anguish have nuances in their definitions, both can lead to significant distress. Understanding the distinctions and seeking appropriate interventions can greatly improve the quality of life.

Anxiety and anguish are two emotional states that can have a number of anxiogenic effects, meaning that they can increase anxiety symptoms.

8.3 Anxiogenic effects of anxiety

Some of the anxiogenic effects of anxiety include:

- Increased heart rate and blood pressure

- Sweating

- Trembling

- Shortness of breath

- Chest pain

- Dizziness

- Nausea

- Difficulty concentrating

- Irritability

- Restlessness

- Muscle tension

- Avoidance of feared situations

8.4 Anxiogenic effects of anguish

Anguish is a more severe form of anxiety that can be characterized by feelings of intense distress, fear, and despair. Some of the anxiogenic effects of anguish include:

- All of the anxiogenic effects of anxiety listed above

- A feeling of impending doom

- A feeling of loss of control

- A sense of detachment from oneself or one's surroundings

- Panic attacks

The anxiogenic effects of anxiety and anguish can be debilitating and interfere with all aspects of a person's life. If you are struggling with anxiety or anguish, it is important to seek professional help. A mental health professional can help you understand your condition and develop a treatment plan to manage your symptoms.

8.5 How anxiety and anguish can lead to more anxiety

Anxiety and anguish can lead to more anxiety in several ways. For example, people with anxiety and anguish may start to avoid situations that they fear trigger their anxiety. This can lead to social isolation and decreased activity levels, increasing anxiety symptoms.

Additionally, people with anxiety and anguish may start to worry about their anxiety symptoms and the impact that they will have on their life. This can lead to a vicious cycle, where the anxiety about anxiety leads to more anxiety.

8.6 How to break the cycle of anxiety

There are several things that people can do to break the cycle of anxiety. Some helpful tips include:

- Seek professional help: A mental health professional can help you to understand your anxiety and develop a treatment plan to manage your symptoms.

- Learn relaxation techniques: Relaxation techniques, such as deep breathing and meditation, can help to reduce anxiety symptoms.

- Regular exercise is a great way to reduce stress and anxiety. Aim for at least 30 min of moderate-intensity exercise most days of the week.

- Get enough sleep: When you are well-rested, you are better able to cope with stress and anxiety. Aim for 7–8 h of sleep per night.

- *Eat a healthy diet*: Eating a healthy diet can help to improve your mood and reduce anxiety symptoms. Avoid processed foods, sugary drinks, and excessive caffeine and alcohol.

- *Identify and challenge negative thoughts*: People with anxiety often have negative thoughts and beliefs about themselves and their world. These thoughts can contribute to anxiety symptoms. Learning to identify and challenge these negative thoughts can help reduce anxiety.

- *Gradually expose yourself to feared situations*: One of the best ways to overcome anxiety is to progressively expose yourself to the situations you fear. This is called exposure therapy, and it can effectively reduce anxiety symptoms.

If you are struggling with anxiety and anguish, please know you are not alone. Many people experience these conditions, and there is effective treatment available. Please reach out to a mental health professional for help.

9. Conclusion

Anxiety and anguish are two emotional states that can significantly impact a person's life. Anxiety is a feeling of worry, nervousness, or unease, while anguish is a more severe form of anxiety characterized by intense distress, fear, and despair.

Various factors, including stress, trauma, and genetics, can cause anxiety and anguish. They can also be symptoms of other mental health conditions, such as depression and post-traumatic stress disorder (PTSD).

Anxiety and anguish, convoluted psychological phenomena, intertwine with the fabric of human existence, influenced by diverse anthropological factors. The amalgamation of philosophical, relational, and anthropological studies unravels the diversified tapestry of anxiety expressions and experiences. From pediatric populations to cultural contexts, exploring anxiety necessitates a holistic, integrative approach, recognizing the complexity and uniqueness of individual and collective experiences. Enhanced understanding and innovative interventions are pivotal in navigating the intricate domains of anxiety and anguish, fostering well-being and resilience in diverse populations.

Anxiety and anguish can have several negative effects on a person's life. They can interfere with work, school, relationships, and other activities of daily living. Anxiety and anguish can also lead to physical health problems, such as headaches, stomachaches, and insomnia.

If you are struggling with anxiety or anguish, it is important to seek professional help. A mental health professional can help you understand your condition and develop a treatment plan to manage your symptoms. Treatment for anxiety and anguish may include therapy, medication, or a combination of both.

Here are some additional tips for coping with anxiety and anguish:

- Get regular exercise. Exercise is a great way to reduce stress and anxiety. Aim for at least 30 min of moderate-intensity exercise most days of the week.

- Get enough sleep. When you are well-rested, you are better able to cope with stress and anxiety. Aim for 7–8 h of sleep per night.

- Eat a healthy diet. Eating a healthy diet can help to improve your mood and reduce anxiety symptoms. Avoid processed foods, sugary drinks, and excessive caffeine and alcohol.

- Learn relaxation techniques. Relaxation techniques, such as deep breathing and meditation, can help to reduce anxiety symptoms.

- Identify and challenge negative thoughts. People with anxiety often have negative thoughts and beliefs about themselves and the world around them. These thoughts can contribute to anxiety symptoms. Learning to identify and challenge these negative thoughts can help to reduce anxiety.

- Gradually expose yourself to feared situations. One of the best ways to overcome anxiety is to progressively expose yourself to the situations you fear. This is called exposure therapy, and it can effectively reduce anxiety symptoms.

Remember, you are not alone. Anxiety and anguish are common mental health conditions affecting millions of people worldwide. Effective treatment is available, so please get in touch with a mental health professional for help.

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Section 3

Social Perspective

Chapter 5

Trait Anxiety and Health Attitude, Risk Factor Awareness, and Prevention of Cardiovascular Disease: A Study among the 25–44-Year-Old of Novosibirsk

Valery V. Gafarov, Elena A. Gromova, Ksenija A. Strigaleva, Igor V. Gagulin and Almira V. Gafarova

Abstract

To analyze the association between trait anxiety and health attitude, awareness of risk factors, and prevention of cardiovascular disease in men and women aged 25–44 years. In 2013–2016, 427 men and 548 women of residents 25–44 years were studied. To assess TA (trait anxiety), a form of Spielberger's self-report Trait Anxiety Inventory has been proposed. When interpreting the indicators, the following approximate estimates of anxiety were used: low TA (LTA), medium TA (MTA), and high TA (HTA). The framework of the budget issue Reg. No.122031700094-5. Respondents with HTA believed that they were "not quite healthy"; had complaints about their health; apparently did not take enough care of their health. People with HTA believed that it was "highly likely" that they would get a serious disease in the next 5–10 years. It turned out that only 5.1% of the population planned to consult a doctor with HTA, less than people with LTA - 12.1% (p < 0.05). It has been established that trait anxiety is associated with low self-esteem regarding one's health status and insufficient awareness of both risk factors and prevention of CVD.

Keywords: trait anxiety, health attitude, CVD risk factor awareness, CVD prevention attitudes, men, women

1. Introduction

In the DSM-5 [1], anxiety is defined as the expectation of a future threat and is distinguished from fear, which is an emotional response to a real or perceived imminent threat. In addition, the term "anxiety" in DSM-5 adds an additional nuance, referring to the cognitive aspects of anxious expectation. Anxiety is a normal emotion. From an evolutionary perspective, it is adaptive because it promotes survival by encouraging people to avoid dangerous places. Since the twentieth century, anxiety

has been considered a disorder in psychiatric classifications. The clinical threshold between normal adaptive anxiety in everyday life and unbearable pathological anxiety requiring treatment is the subject of clinical evaluation [2].

Mood disorders, especially melancholy, may have historical roots dating back to classical antiquity. The philosophical writings of the Latin Stoics, such as the treatises of Cicero and Seneca, are the prototype of many modern views of the clinical features and cognitive treatment of anxiety [3]. Nevertheless, the anxious affect is distinct from sadness; moreover, anxiety is defined as a somatic disease [3]. In Cicero's time, Roman authors created new terms for philosophical and medical concepts and turned to original Greek words to define these neologisms. For the first time, Cicero makes an interesting distinction between *anxiety*, which refers to trait anxiety or the fact of a tendency to be anxious, and *anger*, which refers to state anxiety or situational anxiety. This anticipates the work of Cattell and Schleier, who are often credited with introducing the terms "state" and "trait" of anxiety [4].

Anxiety in humans is a complex phenomenon and is characterized by specific cognitive, affective, and behavioral responses at the level of the holistic personality, depending on the degree of severity in the individual emotional space to objective and subjective sources of threat [5, 6].

The analysis of ideas about the functions of anxiety is fundamental to a complete study of its manifestations. If we turn to the functional approach to the study of anxiety as a subjective factor affecting the course of activity, we consider three main functions of this emotional state: signaling, search, and evaluation [7].

The signaling function of the state of anxiety is to anticipate one or another type of danger, to predict something unpleasant, threatening, and to signal it to the individual [8]. Charles Darwin considered the emotions of fear-anxiety and anger-rage to be universal characteristics of animals and humans. He believed that these emotions ensured successful adaptation to changing environmental conditions and survival in the process of natural selection [9]. S. Freud defined anxiety as a specific, unpleasant emotional state accompanied by experiential, physiological, and behavioral components. In his theory, he equated fear with objective anxiety, expressing an emotional response proportional in intensity to the real threat from the environment, and used the term "neurotic anxiety" to describe hypertrophied emotional responses not comparable to the level of objective threat. According to Freud, anxiety acts as an indicator of the presence of a situation "threat perceived presence of threat" both from external sources and from one's own repressed thoughts and experiences, causing an unpleasant emotional state that further serves as a warning to the individual of the need for some form of adaptation. Focusing on the adaptive use of anxiety in motivational behavior, which helps an individual to avoid the threat or cope more effectively with it, the "threat signal" hypothesis by S. Freud is almost consistent with the evolutionary perspective of Ch. Darwin [10].

Proponents of the cognitive approach to analyze emotional behavior view anxiety as an emotional state that arises in response to an undefined, undifferentiated threat [11]. Although the uncertainty of the threat that is the source of the emotion of anxiety can be specified, for example, in the form of an upcoming exam or an anticipated social confrontation, the basic threat is essentially existential because it is in most cases vague and symbolic. We cannot say what will happen, when it will happen, and what will happen next in relation to what has happened, as long as the threat is not associated with a specific event [11]. Dividing human needs into two main types— that of "necessity" and that of "growth" within the framework of the need-informational theory of emotions, P. Simonov considers the low probability of

satisfying any of the needs of necessity to be a source of anxiety, for example, in food, housing, means of protection from harmful influences, ensuring individual, and species existence, etc. [12]. The emergence of the emotion of anxiety is accompanied by an increase in feelings of psychological uncertainty and, to varying degrees of severity, feelings of helplessness. Anxiety is rather an emotion of anticipation of a possible confrontation or potential harm [12].

The search function of anxiety consists in inducing an active search for its sources and manifests itself in a "scanning" of the present situation in order to identify the "stressful elements" of the environment [13]. Psychosomatic and psychopathological disorders are directly related to the chronic urge to search for danger, which is driven by anxiety [14]. In turn, the activity manifested in the search for a threat object is a way of reducing anxiety. In this regard, there may be a strong urge to specify the source of anxiety and its externalization (orientation outside the self), since it is easier to cope with a differentiated, albeit often illusory, threat than with an unknown one. The urge to locate a specific source of threat can transform the emotion of anxiety into an emotion of anger, especially when it comes to protecting oneself from self-humiliation or anticipated harm [14].

One of the fundamentally important functions of anxiety is the function of evaluation of the current situation. Negatively colored emotional experiences of anxiety arise when an individual perceives a situation as dangerous and does not have ready-made, sufficiently reliable ways of dealing with it. The results of the processes of analyzing the significance of the situation and forming attitudes to it generate a cascade of various forms of adaptive activity at the informational, physiological, and behavioral levels, the purpose of which is to eliminate sources of potential threat [15].

Finally, the result of the assessment of the current situation determines not only the degree of severity of the emotion of anxiety, but also the form of the corresponding behavioral reaction or the way of coping with the threatening situation that has arisen [16]. In the simplest case, if the subject interprets the situation as safe during the analysis; the former threat signal loses it signaling function and the fear is eliminated. If danger is confirmed (or not eliminated) due to external or internal (subjective) reasons, the emotion of anxiety is accompanied by motor tendencies of active or passive avoidance (escape) [17].

Within the framework of these tendencies, three forms of behavioral reactions to a dangerous situation are usually distinguished—flight, aggression, and stupor [7], each of which modifies the orientation of the subject's behavior in its own way. In the presence of an insurmountable danger, flight ensures the elimination of the possibility of a collision with a threatening object. If the threatening situation is an obstacle to the satisfaction of needs and is assessed as surmountable, the emotion of anxiety is transformed into the emotion of anger and aggressive behavior leads to the elimination (destruction) of the source of danger. Finally, if aggression and flight are subjectively assessed as impossible to demonstrate, an individual becomes depressed and rejects any activity [18].

Anxiety, defined as a feeling of undefined threat, a feeling of diffuse apprehension and anxious expectation, or undefined disturbance, is the most powerful mechanism of mental stress. Feeling threatened is central to anxiety and determines its biological significance as a signal of distress and danger. Anxiety can play a protective and motivational role similar to that of pain. An increase in behavioral activity, a change in the nature of the behavior, or the involvement of intrapsychic adaptive mechanisms are associated with the occurrence of anxiety [19].

Unlike pain, anxiety is a signal of danger that has not yet been realized. Predicting this is probabilistic and ultimately depends on the individual's characteristics. At the same time, the personal factor often plays a decisive role, and in this case, the intensity of anxiety reflects the individual characteristics of the subject rather than the actual significance of the threat [20]. Anxiety, which is inappropriate in intensity and duration of the situation, prevents the formation of adaptive behavior, and leads to violation of behavioral integration and general disorganization of the human psyche. Thus, anxiety underlies all stress-induced changes in mood and behavior [21].

The anxiety series is an essential element of the process of mental adaptation. It includes (1) a feeling of internal tension that does not have a pronounced shade of threat and serves only as a signal of its approach, causing painful mental discomfort; (2) hyperesthesia, when anxiety and irritability increase and previously neutral stimuli acquire a negative color; and (3) anxiety itself, which is the central element of the series under consideration. It manifests as a sense of undefined threat. A characteristic feature is the inability to determine the nature of the threat, to predict the time of its occurrence. Often there is inadequate logical processing, as a result of which a wrong conclusion is drawn due to a lack of facts. (4) fear anxiety, focused on a certain object. Although the objects associated with anxiety may not be its cause, the subject gets the idea that anxiety can be eliminated by certain actions.

(5) A sense of the inevitability of an impending catastrophe when an increase in the intensity of anxiety disorders leads the subject to the idea that it is impossible to prevent an impending event; (6) anxiety-fearful excitement when the disorganization caused by anxiety reaches a maximum, and the possibility of purposeful activity disappears. In paroxysmal increase of anxiety, all these phenomena can be observed during one paroxysm. In other cases, the change is gradual [10].

Thus, a certain amount of anxiety is a natural and obligatory feature of an active personality. Each person has their own optimal, or desirable, level of anxiety—the so-called helpful anxiety. Individuals classified as highly anxious tend to perceive a threat to their self-esteem and vital activity in a wide range of situations and react with a very pronounced state of anxiety [22].

But the existential resonance of anxiety is much more than methodological. The first thing to grasp is that anxiety does not mean ceaselessly fretting or fitfully worrying about something or other. On the contrary, Heidegger says that anxiety is a rare and subtle mood and in one place he even compares it to a feeling of calm or peace. It is in anxiety that the free, authentic self-first comes into existence. In order to understand what Heidegger means by anxiety, we have to distinguish it from another mood he examines: fear. Heidegger gives a phenomenology of fear earlier in Being and Time. His claim is that fear is always fear of something threatening, some particular thing in the world. Fear has an object and when that object is removed, I am no longer fearful. Matters are very different from anxiety. If fear is fearful of something particular and determinate, then anxiety is anxious about nothing in particular and is indeterminate. If fear is directed toward some distinct thing in the world, spiders or whatever, then anxiety is anxious about being in the world as such. Anxiety is experienced in the face of something completely indefinite. It is, Heidegger insists, "nothing and nowhere" [23].

Anxiety is a factor that can manifest itself as an adaptive component in an acute stressful situation; with prolonged exposure to stressful factors, the anxiety reaction is considered as a pre-nosological syndrome, leading to the development of psychosomatic pathology. The syndrome of psychoemotional tension has been described, manifested by an increased level of personal and reactive anxiety, a decrease in emotional

stability, the level of social adaptation and frustration tolerance, a predominance of the tone of the sympathetic system with changes in hemodynamics, increased activity of the hypothalamic-pituitary-adrenal system, an increase in lipid content and a shift in the lipoprotein spectrum toward atherogenic fractions. Similar changes have been observed in the study of emotional distress and adaptation to stress [19].

With sufficient semantic uncertainty of the term "anxiety" in psychological and psychophysiological studies, it is most often used in two main meanings that are related but refer to different concepts—as a mental state (state anxiety) and a personality trait (trait anxiety) [24]. Building on a series of pioneering factor analytic studies by Cattell that first identified relatively independent factors of situational and trait anxiety, and on Freud's threat signal theory, Spielberger et al. developed and substantiated ideas about anxiety as a two-factor construct. It turned out that physiological changes (such as heart rate or blood pressure) that fluctuate over time contribute more to situational anxiety and significantly less to trait anxiety. Conversely, most psychometric assessment scales show high stability over time and make an overwhelming contribution to the factor of trait anxiety. Thus, although situational and trait anxiety are positively correlated, they are logically distinct constructs [17].

Currently, the term "situational anxiety" is used to describe an unpleasant emotional state that occurs in a situation of uncertain danger or threat, characterized by subjective feelings of tension, expectation of unfavorable development of events, and combined with symptoms of activation of the autonomic nervous system. Situational anxiety varies in intensity and changes over time, depending on the perceived conscious, unconscious, or psychological threat. At the same time, the term "anxiety" as a personality trait characterizes a relatively stable degree of severity of the perception of a threat to one's self in various situations and a tendency to respond to them by increasing the state of anxiety. Trait anxiety is understood as a stable individual trait that reflects a person's predisposition to anxiety and suggests that he or she has a tendency to perceive a fairly wide range of situations as threatening and to respond to each of them in a particular way. As a predisposition, trait anxiety is activated when certain stimuli are experienced by a person as dangerous to his or her sense of self-worth [6]. At the psychological level, its manifestations are always individualized when exposed to different stressors. A highly anxious person tends to perceive the surrounding world as potentially threatening or dangerous to a much greater extent than a low anxious person [9].

For the analysis of neuropsychological and psychophysiological mechanisms of anxiety as an emotion and as a personal determinant, the most commonly used representations of J. Gray on three neuropsychological systems that play an important role in the control of emotional behavior: Approach System, Fight/Flight System, and Behavioral Inhibition System [25, 26]. The Approach System is associated with conditional reinforcement (or non-punishment) and is aimed at increasing the likelihood of repetition of the action in the future. The Fight/Flight System is associated with unconditional punishment. The Behavioral Inhibition System—with conditional punishment or lack of reinforcement. The balance between the levels of reactivity of these three systems determines the typological characteristics of the individual. High-trait anxiety is more likely to correspond to increased activity in the Behavioral Inhibition System than to a deficit in the Achievement System. In other words, anxiety is more characterized by an increased sense of threat rather than a weakening of the sense of satisfaction. Since individual differences in the reactivity of the Behavioral Inhibition System can determine the level of trait anxiety, it is necessary to dwell in more detail on the functions of this system.

The Behavioral Inhibition System organizes responses to conditioned aversive stimuli based on their association with punishment or positive non-reinforcement. All three types of responses or "outputs" of the Behavioral Inhibition System (behavioral inhibition, increased attention, and an increase in the level of nonspecific activation), regardless of the "input" (novelty; stimuli associated with punishment; stimuli associated with positive non-reinforcement), are blocked by antianxiety agents.

Presumably, the Behavioral Inhibition System plays an important "tracking" role so that the behavior is carried out "according to plan." When real events coincide with the predicted ones, the system continues to work only in "tracking" mode, and the behavior remains under the control of other brain mechanisms. However, in the case of an unpredicted event, the absence of a predicted event, or if the next predicted event is aversive (associated with punishment or positive non-reinforcement), the system switches to the "control" mode of behavior, causing one of its characteristic responses: inhibition of the current behavior, increased attention, or an increase in the level of nonspecific activation. These behavioral inhibition functions correlate with key features of high-trait anxiety and its clinical manifestations [24]. High-trait anxiety in healthy individuals is characterized by increased sensitivity to stimuli associated with punishment or lack of positive reinforcement (inputs to the behavioral inhibition system). In the case of clinical manifestations of anxiety, phobic behavior is mainly associated with the output of the behavioral inhibition system in the "control" mode, and obsessive-compulsive symptoms are associated with excessive tracking of the system in the "tracking" mode. Finally, in subjects with panic attacks, the parameter corresponding to the sum of the activity of the behavioral inhibition and fight/flight systems should prevail. At the same time, panic attacks are characteristic of patients with chronic activity in both Fight/Flight and Behavioral Inhibition systems [24]. Using Aizenkov's three-dimensional personality space with factors of extraversion, neuroticism, and psychoticism, J. Gray suggested that the selected parameters may reflect, albeit indirectly, the activity of the three neuropsychological emotional systems discussed above, and that high-trait anxiety, reflecting the reactivity of the Behavioral Inhibition System, is at the same pole as high neuroticism, high introversion, and low psychopathy.

While J. Gray's model has an important theoretical significance, the experimental analysis of psychometric assessments of anxiety as a trait and as a state, as subjective manifestations of the tonic and phasic forms of the passive defense reflex, in reciprocal relationships with the forms of which the tonic and phasic orientation reflexes as respectively [25, 26], is of great interest. It is common knowledge that in humans, the tonic defensive reflex resulting from the action of a threatening stimulus is expressed by an increase in heart rate, in contrast to the phasic orientation response, which is characterized by a decrease in heart rate [27]. When comparing high and low anxiety subjects according to the characteristics of heart rate and R-R interval variability, it was found that the state of high anxiety subjects at rest is close to the state of low anxiety subjects during information load [27]. The researchers interpret such a physiological characteristic of highly anxious subjects as a manifestation of the strengthening of the tonic form of the passive-defensive reflex, which is constantly observed both at rest and during information load. Besides, the tonic defensive reflex is represented subjectively by high-trait anxiety and objectively by high heart rate, high value of stress index, and decrease in variability of R-R intervals. At the same time, the group of people with low trait anxiety is characterized by a greater contribution of the orientation reflex, which corresponds to a lower heart rate and a greater variability of R-R intervals both in the background and with information load [28].

Over the past decade, there has been increased research interest in anxiety disorders, largely due to increased recognition of the burden and consequences associated with untreated illness [29]. Untreated anxiety is associated with significant personal and societal costs, including frequent primary and emergency care visits, reduced work productivity, unemployment, and impaired social relationships [29].

Self-rated health is "a summary statement about how numerous aspects of health, both subjective and objective, are combined in the perception of an individual respondent" and is a powerful indicator of people's health status. Self-rated health is related to age, gender, education level, marital status, socioeconomic status, social environment, support, and behaviors that affect physical and mental health. In addition, a relationship has been found between self-rated health and objective health, which is a reliable predictor of people's health status because it combines objective knowledge about possible medical conditions with the interpretation of a person's physical and mental indicators [30].

Self-rated health is a reliable indicator of objective health [31], as it combines objective knowledge of potential medical conditions with the interpretation of physical and mental indicators of a person [32]. This allows for a general assessment of the respondent's overall health but has also been associated with the prediction of mortality [33–35]. The reliability of this type of self-report has been defined as good or even better than indicators related to chronic disease, functional ability, and psychological well-being [36], and is also prognostic for aspects such as the incidence of chronic disease [33, 37] and functional decline in the work of organs and systems [37, 38].

Studies show that a more comprehensive understanding of health [39] includes not only the absence of health problems but also other possible determinants related to physical fitness and general well-being [40]. This is consistent with the WHO definition of health, which refers not only to the absence of disease or disability, but also to a state of complete physical, mental, and social well-being [41]. Studies have shown that the absence of limitations in daily activities is an important determinant of functional health status [42, 43] and the number of chronic diseases and pain [44]. In addition, not only has psychological well-being been associated with health perceptions [37], particularly self-esteem, distress, and depression [44], but also with cognitive functioning [45].

The problem of public participation in preventive programs aimed at changing behavioral habits is still relevant, since the absence of an elementary "health culture," together with stress and an unfavorable environmental situation repeatedly increases the risks of morbidity and mortality [22].

However, the success of preventive programs depends not only on the efforts of medical professionals but also on the conscious desire of the individual to change his or her behavioral stereotypes. A kind of indicator of such aspirations is health attitude, which is considered one of the main sociopsychological factors influencing the activity of the population in population projects for the primary prevention of CND [46].

It is possible to characterize health attitude as the result of a set of relations that characterize a given society at a certain stage of its development. A related issue is the identification of factors that have an impact on health attitudes. There are general factors, which are determined by the economic situation, sociopolitical system of a society, peculiarities of its culture and ideology, and specific factors, which include the state of health, lifestyle characteristics, health awareness, influence of family, school, health system, etc. These factors are refracted in the structure of the personality of the individual—the bearer of a certain attitude to health, or this refraction is carried out in the structure of mass consciousness, forming certain norms of behavior

in the field of health [47]. The most traditional is the study of the conditionality of health attitude by such sociodemographic characteristics of an individual as gender, age, level of education, skill level, marital status, etc. This is due to the fact that in lifestyle change issues, the best results are achieved when information is targeted to clearly defined groups of the population according to their social status [48]. Effective disease prevention is facilitated by factors such as medical and health literacy, positive attitudes toward preventive measures, and the ability to change habits. On the other hand, the social environment and sustainable models of public culture are factors that can counteract prevention and contribute to maintaining the status quo at the public level [48]. Therefore, it is necessary to develop and implement modern preventive programs created within the framework of the biopsychosocial model of health and health care [22].

Taking into account the above facts, it is of interest to study the associative relationship between trait anxiety and health attitude, prevention of CVD, and awareness of CVD risk factors among people aged 25–44 in Novosibirsk.

2. Materials and methods

A screening study of a representative sample of the population aged 25–44 years was conducted in one of the districts of Novosibirsk (budget issue No. Reg. no. 122031700094-5) in 2013–2016. A total of 975 subjects were examined, males n = 427, mean age 34 ± 0.4 years, response - 71%; females n = 548, mean age 35 ± 0.4 years, response - 72%.

The general examination was performed according to the standard methods of the WHO program "MONICA-psychosocial (MOPSY)" [49]. Self-assessment of health status, attitudes toward preventive methods, and health-related behaviors were assessed using the knowledge and attitudes toward one's health questionnaire. To assess TA (trait anxiety), a form of Spielberger's self-report scale has been proposed [16], consisting of 20 statements. For each statement, four levels of intensity are provided: 1 – "hardly ever," 2 – "sometimes," 3 – "often," and 4 – "almost always." When analyzing the results of the self-report, it was assumed that the final total score could range from 20 to 80 points. Also, the higher the final indicator, the higher the TA level. When interpreting the indicators, the following approximate estimates of anxiety were used: up to 30 points - low TA (LTA), 31–44 points - medium TA (MTA), 45 or more - high TA (HTA).

Individuals who completed the questionnaire incorrectly were excluded from analysis. The SPSS version 20 software package was used for statistical analysis [50]. Pearson's chi-squared criterion χ^2 was used to test the statistical significance of the differences between the groups [51]. A significance level of $p < 0.05$ was assumed.

3. Results

The relationship between personal anxiety and health attitudes, health screening, medical care and disease prevention, and awareness of CVD risk factors was examined.

To the question: "How do you rate your health?," the answer "Not quite healthy" was more frequent among people with HTA than with LTA, both in the population (62.8 and 32%) and among men (57.1 and 26.7%) and women (64.9 and 37.1%). On the contrary, the number of those who considered themselves "healthy" was higher

among those with LTA than among those with HTA, both in the population (36.8 and 21.8%), as well as among men (43.8 and 33.3%) and women (29.9 and 17.5%) (χ^2 = 52,965 df = 8 p < 0.0001 -population, χ^2 = 17.629 df = 8 p < 0.05 -male χ^2 = 34.993 df = 8 p < 0.001 female) (**Table 1**).

Among people with HTA, both the population (74.4%) and men (76.2%) answered the question: "Do you have any health complaints?," they answered in the affirmative more often than those with LTA (52.9 and 52.3%, respectively) in contrast to women. It was found among them that in women with MTA (77.5%) and HTA (73.7%) the affirmative response was more frequent than in women with LTA (52.3%) (χ^2 = 43.140 df = 2 p < 0.001-population, χ^2 = 9.737 df = 2 p < 0.01-male, χ^2 = 35.029 df = 2 p < 0.001-female) (**Table 1**).

To the question: "Do you think you take enough care of your health?," the majority of people with HTA, both in the population (29.5%) and among women (29.8%), were more likely to say "apparently not enough" compared with people with LTA (13.8 and 12.2%). Among men in the population with both HTA (28.6%) and MTA (29.7%), the answer "apparently not enough" was more prevalent than among those with LTA (15.3%) (χ^2 = 33.191 df = 4 p < 0.001-population, χ^2 = 13.382 df = 4 p < 0.010-male, χ^2 = 24.966 df = 4 p < 0.001-female) (**Table 1**). 1. (Awareness, attitudes toward health, and trait anxiety in aged 25–44 years old)

Analyzing the question: "Do you think that a healthy person of your age can get a serious disease in the next 5–10 years?," it turned out that in the population with HTA, the largest proportion of respondents - 41% said "highly likely," compared with LTA - 27.8% and MTA - 37.1%. Among women in the population, the proportion of people who answered "highly likely" was high both among women with MTA (41.9%) and with HTA (38.6%), compared with LTA (28.5%). No obvious differences were found among men (χ^2 = 15.460 df = 4 p < 0.01 population, χ^2 = 4.288 df = 4 p 0.05 - male, χ^2 = 14.853 df = 4 p < 0.01 - female) (**Table 2**).

As for the answers to the question: "Do you think that a healthy person of your age can avoid some serious diseases by taking preventive measures in advance?," no significant differences were found between groups differing in the level of TA, both in men and women and in the general population (χ^2 = 4.289 df = 4 p<0.05-population, χ^2 = 1.380 df = 4 p <0.05-men, χ^2 = 7.989 df = 4 p< 0.05-female) (**Table 2**).

When it comes to the questions: "Do you believe that modern medicine can prevent heart disease?" (χ^2 = 11.525 df = 8 p<0.05-population., χ^2 = 4.339 df = 8 p< 0.05-male, χ^2 = 12.463 df = 8 p< 0.05-female) and "Do you think that it is currently possible to successfully treat all heart diseases?" (χ^2 = 10,758 df = 8 p< 0.05-population, χ^2 = 4072 df = 6 p< 0.05-male, χ^2 = 13,231 df = 8 p< 0.05-female). We found no differences in the responses of people with different TA levels (**Table 2**). 2. (Attitudes toward CVD and TA prevention in aged 25–44 years old).

According to the data obtained, from the questionnaire question: "One of middle-aged people's health problems is heart disease. There are different opinions on this. Which opinion is the most acceptable for you?" Among the population, the majority of respondents would only consult a doctor if they had severe pain in the area of the heart—people with LTA (51.8%), MTA (62.2%), and HTA (60.3%). At the same time, 5.1% of respondents with HTA did not expect to see a doctor for any painful condition, even with significant heart pain, compared to 3% of people with LTA. Regardless of pain in the heart area, 6.4% of people with HTA were always willing to see a doctor, which was lower than in people with LTA - 9.4% (χ^2 = 14.144 df = 6 p < 0.05) (**Table 3**).

In addition, the results of the survey revealed the opinion of the population and men regarding trust in the doctor and diagnosis of CVD in respondents with HTA,

Question:	Both genders						Male						Female					
	LTA		MTA		HTA		LTA		MTA		HTA		LTA		MTA		HTA	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1. How do you rate your health?																		
Perfectly healthy	18	4.1	5	1.2	0	0	11	5.1	3	1.8	0	0	7	3.2	2	0.8	0	0
In good health	115	26.3	72	17.3	10	12.8	50	23.0	33	20	2	9.5	65	29.4	39	15.5	8	14
Healthy	161	36.8	130	31.2	17	21.8	95	43.8	58	35.2	7	33.3	66	29.9	72	28.6	10	17.5
Not quite healthy	140	32.0	196	47.0	49	62.8	58	26.7	66	40	12	57.1	82	37.1	130	51.6	37	64.9
Ill	4	0.9	14	3.4	2	2.6	3	1.4	5	3.0	0	0	1	0.5	9	3.6	2	3.5
Total	438	100	417	100	78	100	217	100	165	100	21	100	221	100	252	100	57	100
	χ^2 = 52.965 df = 8 p < 0.0001						χ^2 = 17.629 df = 8 p < 0.05						χ^2 = 34.993 df = 8 p < 0.001					
2. Do you have any health complaints?																		
Yes	230	52.9	307	73.4	58	74.4	115	53.5	111	67.3	16	76.2	115	52.3	196	77.5	42	73.7
No	205	47.1	111	26.6	20	25.6	100	46.5	54	32.7	5	23.8	105	47.7	57	22.5	15	26.3
Total	435	100	418	100	78	100	215	100	165	100	21	100	220	100	253	100	57	100
	χ^2 = 43.140 df = 2 p < 0.001						χ^2 = 9.737 df = 2 p < 0.01						χ^2 = 35,029 df = 2 p < 0.001					
3. Do you think you take enough care of your health?																		
Yes	79	18.1	48	11.5	6	7.7	29	13.5	13	7.9	3	14.3	50	22.6	35	13.8	3	5.3
I could take more care	297	68.1	254	60.8	49	62.8	153	71.2	103	62.4	12	57.1	144	65.2	151	59.7	37	64.9
Apparently not enough	60	13.8	116	27.8	23	29.5	33	15.3	49	29.7	6	28.6	27	12.2	67	26.5	17	29.8
Total	436	100	418	100	78	100	215	100	165	100	21	100	221	100	253	100	57	100
	χ^2 = 33.191 df = 4 p < 0.001						χ^2 = 13.382 df = 4 p < 0.010						χ^2 = 24.966 df = 4 p < 0.001					

Table 1.
Awareness, attitudes toward health, and trait anxiety in those aged 25–44 years old.

Question:	Both genders						Male						Female					
	LTA		MTA		HTA		LTA		MTA		HTA		LTA		MTA		HTA	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
4. Do you think that a healthy person of your age can get a serious disease in the next 5–10 years?																		
Highly likely	121	27.8	155	37.1	32	41	58	27.0	49	29.7	10	47.6	63	28.5	106	41.9	22	38.6
Likely	299	68.6	250	59.8	40	51.3	149	69.3	109	66.1	10	47.6	150	67.9	141	55.7	30	52.6
Unlikely	16	3.7	13	3.1	6	7.7	8	3.7	7	4.2	1	4.8	8	3.6	6	2.4	5	8.8
Total	436	100	418	100	78	100	215	100	165	100	21	100	221	100	253	100	57	100
	$\chi^2 = 15.460$ df = 4 p < 0.01						$\chi^2 = 4.288$ df = 4 p > 0.05						$\chi^2 = 14.853$ df = 4 p < 0.01					
5. Do you think that a healthy person of your age can avoid some serious diseases by taking preventive measures in advance?																		
Yes, absolutely	299	68.7	296	70.8	52	66.7	149	69.6	118	71.5	14	66.7	150	67.9	178	70.4	38	66.7
Maybe yes	134	30.8	117	28.0	24	30.8	63	29.4	44	26.7	7	33.3	71	32.1	73	28.9	17	29.8
Unlikely	2	0.5	5	1.2	2	2.6	2	0.9	3	1.8	0	0	0	0	2	0.8	2	3.5
Total	435	100	418	100	78	100	214	100	165	100	21	100	221	100	253	100	57	100
	$\chi^2 = 4.289$ df = 4 p > 0.05						$\chi^2 = 1.380$ df = 4 p > 0.05						$\chi^2 = 7.989$ df = 4 p > 0.05					
6. Do you believe that modern medicine can prevent heart disease?																		
Yes, all types of heart disease	65	14.9	52	12.4	17	21.8	37	17.2	22	13.3	4	19	28	12.7	30	11.9	13	22.8
Yes, most types of heart disease	194	44.5	179	42.8	22	28.2	101	47	75	45.5	8	38.1	93	42.1	104	41.1	14	24.6
Depending on the disease	147	33.7	149	35.6	31	39.7	59	27.4	55	33.3	6	28.6	88	39.8	94	37.2	25	43.9
No, only some disease	28	6.4	36	8.6	7	9.0	17	7.9	13	7.9	3	14.3	11	5.0	23	9.1	4	7.0

Question:	Both genders						Male						Female					
	LTA		MTA		HTA		LTA		MTA		HTA		LTA		MTA		HTA	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No, not a single type of disease	2	0.5	2	0.5	1	1.3	1	0.5	0	0	0	0	1	0.5	2	0.8	1	1.8
Total	436	100	418	100	78	100	215	100	165	100	21	100	221	100	253	100	57	100
	$\chi^2 = 11.525$ df = 8 p > 0.05						$\chi^2 = 4.339$ df = 8 p > 0.05						$\chi^2 = 12.463$ df = 8 p > 0.05					

7. Do you think that it is currently possible to successfully treat all heart diseases?

	Both genders						Male						Female					
	LTA		MTA		HTA		LTA		MTA		HTA		LTA		MTA		HTA	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Yes, all of them	37	8.5	47	11.2	11	14.3	26	12	21	12.7	3	14.3	11	5	26	10.3	8	14.3
Yes, most types of heart disease	257	58.8	218	52.2	33	42.9	121	56	90	54.5	9	42.9	136	61.5	128	50.6	24	42.9
Depending on the disease	137	31.4	143	34.2	31	40.3	67	31	49	29.7	8	38.1	70	31.7	94	37.2	23	41.1
No, just some disease	6	1.4	9	2.2	2	2.6	2	0.9	5	3	1	4.8	4	1.8	4	1.6	1	1.8
No, not a single type of disease	0	0	1	0.2	0	0	0	0	0	0	0	0	0	0	1	0.4	0	0
Total	437	100	418	100	77	100	216	100	165	100	21	100	221	100	253	100	56	100
	$\chi^2 = 10{,}758$ df = 8 p < 0.05						$\chi^2 = 4072$ df = 6 p < 0.05						$\chi^2 = 13{,}231$ df = 8 p < 0.05					

Table 2.
Attitudes toward CVD and TA prevention in aged 25–44 years old.

8. One of middle-aged people's health problems is heart disease. There are different opinions on this. Which opinion is the most acceptable for you?

Question:	Both genders						Male						Female					
	LTA		MTA		HTA		LTA		MTA		HTA		LTA		MTA		HTA	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Regardless of whether or not I have pain or discomfort in the heart area, I have regular check-ups with a doctor.	41	9.4	28	6.7	5	6.4	22	10.2	6	3.6	2	9.5	19	8.6	22	8.7	3	5.3
I see the doctor whenever I have heart pain or discomfort.	156	35.8	111	26.6	22	28.2	71	32.9	42	25.5	6	28.6	85	38.6	69	27.3	16	28.1
I would go to a doctor if I had severe pain or an unpleasant sensation in the heart area, but I would not go if the pain or unpleasant sensation was only mild.	226	51.8	260	62.2	47	60.3	115	53.2	108	65.5	12	57.1	111	50.5	152	60.1	35	61.4
Even if I had severe pain or an unpleasant sensation in the heart area, I would not go to a doctor.	13	3	19	4.5	4	5.1	8	3.7	9	5.5	1	4.8	5	2.3	10	4	3	5.3
Total	436	100	418	100	78	100	216	100	165	100	21	100	220	100	253	100	57	100
	χ^2 = 14.144 df = 6 p < 0.05						χ^2 = 10.286 df = 6 p > 0.05						χ^2 = 9.644 df = 6 p > 0.05					

9. People have different opinions about modern methods of diagnosing heart disease. Which opinion do you agree with?

Question:	Both genders						Male						Female					
	LTA		MTA		HTA		LTA		MTA		HTA		LTA		MTA		HTA	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
I trust the way I feel. If I feel good, it means I'm not ill.	105	24	106	25.4	15	19.2	62	28.7	49	29.9	3	14.3	43	19.5	57	22.5	12	21.1
A doctor knows better. If he/she does a checkup on me and tells me that I am healthy or sick, I trust him/her.	141	32.3	125	30	25	32.1	71	32.9	51	31.1	5	23.8	70	31.7	74	29.2	20	35.1
Until thorough research is done by specialists, I will not necessarily agree with the doctor's opinion after a general examination.	191	43.7	186	44.6	37	47.4	83	38.4	64	39	12	57.1	108	48.9	122	48.2	25	43.9
Total	437	100	417	100	78	100	216	100	164	100	21	100	221	100	253	100	57	100
	$\chi^2 = 12.593$ df = 6 p < 0.05						$\chi^2 = 21.943$ df = 6 p < 0.001						$\chi^2 = 1.359$ df = 4 p > 0.05					

Question:

10. Have you had any pleasant experiences with medical care?

	Both genders						Male						Female					
	LTA		MTA		HTA		LTA		MTA		HTA		LTA		MTA		HTA	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Never	127	29.5	92	22.2	10	12.8	73	34.6	43	26.4	2	9.5	54	24.7	49	19.5	8	14
Once or twice	101	23.5	101	24.4	26	33.3	55	26.1	45	27.6	11	52.4	46	21	56	22.3	15	26.3
Several times	160	37.2	175	42.3	31	39.7	68	32.2	61	37.4	3	14.3	92	42	114	45.4	28	49.1
Often	41	9.5	40	9.7	10	12.8	15	7.1	12	7.4	4	19	26	11.9	28	11.2	6	10.5
Very often	1	0.2	6	1.4	1	1.3	0	0	2	1.2	1	4.8	1	0.5	4	1.6	0	0
Total	430	100	414	100	78	100	211	100	163	100	21	100	219	100	251	100	57	100
	$\chi^2 = 18{,}000$ df = 8 p < 0.05						$\chi^2 = 23{,}109$ df = 8 p < 0.01						$\chi^2 = 6461$ df = 8 p > 0.05					

Table 3.
Attitudes of 25–44 years old toward their health, medical care, and TA.

Question:	Both genders						Male						Female					
	LTA		MTA		HTA		LTA		MTA		HTA		LTA		MTA		HTA	
	n	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
11. If you feel unwell at work, what do you do? (Retired and unemployed answer as if they were working)																		
I continue to work	165	37.8	181	43.3	39	50	80	37	64	38.8	9	42.9	85	38.5	117	46.2	30	52.6
I stop working and rest	219	50.1	208	49.8	35	44.9	111	51.4	95	57.6	12	57.1	108	48.9	113	44.7	23	40.4
I go to the doctor	53	12.1	29	6.9	4	5.1	25	11.6	6	3.6	0	0	28	12.7	23	9.1	4	7
Total	437	100	418	100	78	100	216	100	165	100	21	100	221	100	253	100	57	100
	$\chi^2 = 11.330$ df = 4 p < 0.05						$\chi^2 = 10.256$ df = 4 p < 0.05						$\chi^2 = 5.840$ df = 4 p > 0.05					
12. If you have the flu or a fever, what do you do?																		
I work as usual	116	26.6	117	28.1	35	44.9	64	29.8	48	29.1	10	47.6	52	23.5	69	27.4	25	43.9
I stay at home and do my best to get back to work as soon as possible	215	49.3	223	53.5	27	34.6	99	46	92	55.8	8	38.1	116	52.5	131	52	19	33.3
I stay at home until I feel better	105	24.1	77	18.5	16	20.5	52	24.2	25	15.2	3	14.3	53	24	52	20.6	13	22.8
Total	436	100	417	100	78	100	215	100	165	100	21	100	221	100	252	100	57	100
	$\chi^2 = 15.740$ df = 4 p < 0.01						$\chi^2 = 8.711$ df = 4 p > 0.05						$\chi^2 = 11.026$ df = 4 p > 0.05					

Question:	Both genders						Male						Female					
	LTA		MTA		HTA		LTA		MTA		HTA		LTA		MTA		HTA	
	n	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
13. Do you think it makes sense to get screened?																		
Yes, it is useful	386	88.1	351	84	64	82.1	185	85.3	138	83.6	18	85.7	201	91	213	84.2	46	80.7
Probably yes	47	10.7	62	14.8	13	16.7	29	13.4	24	14.5	3	14.3	18	8.1	38	15	10	17.5
Probably not	4	0.9	5	1.2	1	1.3	3	1.4	3	1.8	0	0	1	0.5	2	0.8	1	1.8
It is not useful	1	0.2	0	0	0	0	0	0	0	0	0	0	1	0.5	0	0	0	0
Total	438	100	418	100	78	100	217	100	165	100	21	100	221	100	253	100	57	100
	χ^2 = 5497 df = 6 p > 0.05						χ^2 = 0,578 df = 4 p > 0.05						χ^2 = 9142 df = 6 p > 0.05					

Table 4.
Attitudes to work, health screening, and TA in aged 25–44 years.

LTA, and MTA. About half of the respondents among the population – 47.4% with HTA, trusted specialized research more than just a doctor's examination, compared with men in the population, 57.1% of whom with HTA gave a similar answer. About a third of the respondents among the population with LTA - 32.3% and HTA −32.1% trusted the doctor's examination without additional research, the lowest indicator in this answer option was among men with HTA - 23.8%. At the same time, there was a decrease in trust in their health rate among the respondents. Only 19.2% of respondents with HTA among the population trusted their health rate, compared to 25.4% of those with MTA and 24% of those with LTA. A similar trend was observed among men: those with LTA - 28.7%, MTA - 29.9%, and HTA - 14.3% (χ^2 = 12.593 df = 6 p < 0.05-population χ^2 = 21.943 df = 6 p < 0.001 -male) (**Table 3**).

As the answers to the question: "Have you had any pleasant experiences with medical care?" revealed, fewer (12.8%) in the population with HTA have never experienced positive emotions, compared to LTA - 29.5% and MTA - 22.2%. At the same time, among men with HTA only 9.5% replied this way, which is less than those with LTA - 34.6% (χ^2 = 18.000 df = 8 p < 0.05-population, χ^2 = 23.109 df = 8 p < 0.01 -male) (**Table 3**). 3. (Attitudes of 25–44 years old toward their health, medical care, and TA).

To the question: "If you feel unwell at work, what do you do? (Retired and unemployed answer as if they were working)," it turned out that among the population and among men with LTA and HTA, the frequency of the answer "I continue to work" did not differ significantly from the answer "I go to the doctor." So, among the population, only 5.1% of those with HTA planned to go to the doctor, which is less than among those with LTA - 12.1% (χ^2 = 11.330 df = 4 p < 0.05-general population, χ^2 = 10.256 df = 4 p < 0.05-male) (**Table 4**). Further to the question: "If you have the flu or a fever, what do you do?," the most frequent answer in the population was "I stay at home and do everything to get back to work as soon as possible" with MTA - 53.5%, in contrast to those with HTA - 34.6%. When replying "I work as usual," 44.9% of respondents with a high level of TA answered in the affirmative, which is less among those with LTA - 26.6% (χ^2 = 15.740 df = 4 p < 0.01) (**Table 4**).

The respondents were asked the question: "Do you think it makes sense to get screened?" We did not find significant differences between groups differing in the level of TA, since the overwhelming majority of individuals in the population held the opinion about the benefits of preventive health checks (χ^2 = 5.497 df = 6 p> 0.05-population χ^2 = 0.578 df = 4 p< 0.05 - male, χ^2 = 9.142 df = 6 p< 0.05 - female) (**Table 4**). 4. (Attitudes to work, health screening, and TA in aged 25–44 years).

4. Discussion

The study of psychological and behavioral processes related to health and illness has flourished in recent decades, leading to a number of advances in disease prevention, symptom management, and promotion of healthy behaviors. Anxiety has been found to be particularly important for physical health, with several studies indicating a strong association between anxiety disorders and physical health [52], as well as between the constructs underlying many anxiety disorders, such as anxiety sensitivity (i.e., fear of anxiety-related sensations) and chronic disease [53]. In addition, anxiety-related traits, symptoms, and disorders have been associated with lower engagement in healthy behaviors [54] and higher engagement in unhealthy behaviors [55].

More broadly, anxiety is becoming a phenomenon of increasing importance in health psychology [56]. Among mental disorders, anxiety and depression are considered the leading disorders [57] with a high likelihood of increased emerging health anxiety [58]. Health anxiety is defined as anxiety and fear due to a perceived threat to one's health. It is conceptualized as a multidimensional construct on a continuum ranging from lack of health awareness to disordered health anxiety, such as illness anxiety disorder [59–61]. Trait anxiety may influence perceptions of the disease and, consequently, the need for medical care and attitudes toward prevention programs [62].

Therefore, studying the influence of trait anxiety on how objective and subjective health indicators change in the young population is very relevant and reflects the needs of this population in the prevention of CVD [63]. For example, a significant proportion of respondents in our population, both men (62.8%) and women (64.9%) with high levels of anxiety, believed that they were not completely healthy or had complaints about their health: 76.2% of men and 73.7% of women. Of course, caring for your own health serves an important adaptive function—it helps you survive. Timely elimination of the symptoms of the disease is useful, but some people become overly concerned about their health and have anxiety that varies from mild to extreme [64].

People with high levels of anxiety in our population were more likely to believe that they were not taking enough care of their health, both men (28.6%) and women (29.8%); they believed that there was a high probability that they could get a serious illness in the next 5 or 10 years. That is, high levels of anxiety increase the need for medical care [65], increase the risk of prolonged sickness absence [66], and are a persistent condition if left untreated [67].

One of the types of health-related behavior that has received considerable attention in the context of anxiety is seeking medical help or contact with a medical professional or institution [68]. It is believed that people with anxiety disorders experience a greater number or severity of physical health problems, are more likely to mistake somatic or anxiety-related sensations for medical symptoms, or are more likely to respond to health-related concerns. However, there are no studies found that were aimed at understanding the extent to which anxiety disorders may also be associated with avoidance, delayed treatment, or inconsistent medical treatment, although some data seem to indicate that they are related in some cases [69]. This gap in the literature is surprising given the central role of avoidance, including both behavioral avoidance of anxiety-provoking stimuli and avoidance of internal alarm signals, in the development and maintenance of anxiety disorders [70]. Theoretically, many anxious individuals who tend to fear the somatic sensations associated with anxiety, or who have specific health-related fears, may prefer to avoid potentially threatening information from a clinician related to these feelings and problems; rather than reducing anxiety by seeking support from a doctor, they may prefer to postpone a visit or avoid seeing a doctor altogether [71]. This fully explains the fact that the opinion of our population that they would go to the doctor only in case of severe heart pain, and that this answer does not correlate with the level of anxiety, was found to be similar in the Tyumen sample [71]. More than half of Tyumen women, regardless of age, would go to a doctor only if they had severe pain in the heart area, and only a third—if they had any pain or unpleasant sensation in the heart area [71].

Among people with a high level of trait anxiety, about half of the population (47.4%) and more than half of the men (57.1%) in the population trusted specialized research more than just a doctor's examination; they experienced negative emotions about medical care less often, both among the population (12.8%) and among men

(9.5%). Both overuse and underuse of health care services have important individual and public health consequences: the search for trust and avoidance contribute to the persistence of anxiety and deterioration over time [72, 73], and both can place a burden on the health care system [74], as untimely care can lead to the development of more serious and/or long-term health problems [75].

In conclusion, trait anxiety contributes to low self-rated health, insufficient engagement in preventive health care, and ignorance of CVD risk factors. In other words, high levels of trait anxiety may be associated with delayed, irregular, or inconsistent medical care [43].

5. Conclusions

1. It was found that people with HTA believed that they were "not quite healthy" among the population (62.8%), among men (57.1%), and women (64.9%); had complaints about their health, among population (74.4%), among men in the population (76.2%); believed that they "apparently not enough" care about their health: among the population (29.5%), among men (28.6%), and women (29.8%) in the population.

2. It was found that respondents with HTA believed it was "highly likely" that they could get a serious disease in the next 5–10 years, among the population (41%), among women (38.6%).

3. It was found that people with HTA (60.3%) would go to the doctor only with severe pain in the heart area; regardless of the pain in the heart area, 6.4% of the population were always ready to go to the doctor; they trusted specialized studies more than a doctor's examination among men (57.1%) and among the population (47.4%).

4. It was found that people with HTA were less likely to go to the doctor when they felt unwell at work (5.1%) than those with LTA (12.1%). If they had a high temperature, the most common response among the population with MTA (53.5%) was "I stay at home and do everything I can to get back to work as soon as possible," and "I work as usual" among those with HTA (44.9%).

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Edited by Floriana Irtelli and Fabio Gabrielli

Today, much research is being conducted on the psychological, psychiatric, medical, anthropological, and sociological effects of anxiety and anguish on people's mental and physical health. This book provides a comprehensive overview of this topic by exploring research, theories, biopsychosocial perspectives, and intercultural studies about anxiety and anguish.

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