PSYCHOLOGICAL ISSUES IN AMYOTROPHIC LATERAL SCLEROSIS

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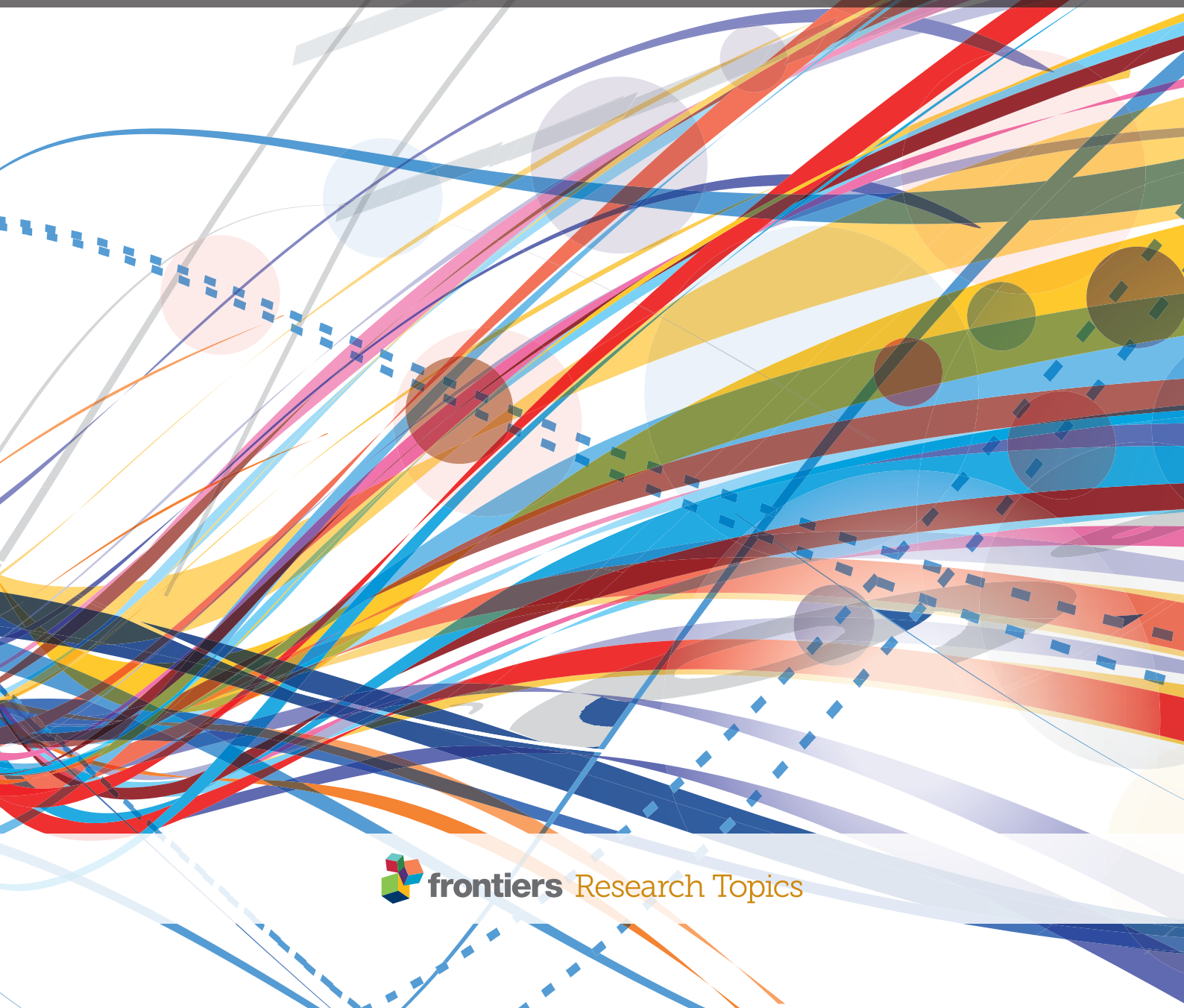

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PSYCHOLOGICAL ISSUES IN AMYOTROPHIC LATERAL SCLEROSIS

Topic Editors:
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Amyotrophic lateral sclerosis is a fatal and progressive disease, characterized by progressive muscles weakness, with consequent loss of physical capacities. Patients become relentlessly immobile and, in the late stages of the disease, develop a "locked-in" state in which only residual muscular movement is possible, but the intellect and the personality usually remain unimpaired. At now, there is no cure for ALS.

The psychological impact of the disease is huge, on both patients and caregivers. Aim of the present Research Topic is to collect new evidence about quality of life, depression, anxiety, pain, spiritual and existential issues, hope and hopelessness in the ALS field, with attention to both patients and their caregivers. Emphasis will be provided to the investigation of psychological support and the possible role of psychologists in this challenging field.

Keywords: Amyotrophic Lateral Sclerosis; Health Psychology; Clinical Psychology, Motor Neuron Disorder; Quality of Life.

Subtopics:

The subtopics to be covered in the Research Topic include, but not limited to:
1. Assessment of psychological variables in ALS
2. Quality of life during the course of the illness
3. Impact of technological assistance to illness (wheelchairs, NIV...)
4. Interfaces among biological, psychosocial, and social factors
5. Psychological and psychotherapeutic interventions
6. Couple and family relationships
7. Research methodology, measurement and statistics
8. Cultural and social features of ALS
9. Professional issues, including training and supervision
10. Implications of research findings for health-related policy

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Table of Contents

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EDITORIAL
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The importance of an idiographic approach for the severe chronic disorders—the case of the amyotrophic lateral sclerosis patient

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The discussion about nomothetic and idiographic approaches is one of the main philosophical debates in the field of psychological sciences (Schafer, 1999; Salvatore and Valsiner, 2010).

The term "nomothetic" comes from the Greek word "nomos" that means "usage, custom, law" and in psychology is referred to the objective classification under similar conditions, to in establish generalizations, such as diagnoses. The term "idiographic" derives from the Greek word "idios", meaning "pertaining to self; one's own, private or separate" and is referred to the aspects of subjective experience that makes each person unique.

In the clinical psychology, the debate deals about the classification of personality and other taxonomies, as well as the use of diagnosis. At the intervention level, the discussion is about the use of individualistic treatment techniques or treatment derived from research where the focus is a group of people with a similar condition, where (individual) efficacy is tested with aggregated statistics. For example, evidence-based research indicates that the cognitive-behavioral therapy has a positive impact toward the anxiety disorders (Olatunji et al., 2010).

As researchers, we look for regularities and repetitive phenomena. However, when the study object is the human being, with all his complexity, we cannot forget that every person is unique. That is even more important in the clinical practice, where clinicians do not have to take care of an "average score," but they must assist an individual, with his clinical peculiarities, thoughts, emotions and relationships.

When dealing with severe and chronic illnesses, such as Amyotrophic Lateral Sclerosis (ALS), this debate is very important and sometimes is at risk of being underestimated. The human tendency toward generalization, together with a superficial approach to research findings, may lead us to stereotypical beliefs about a person living with severe disease. In the case of ALS, an incurable terminal illness with a potentially steep decline in physical function and erosion of independence, it could easily be assumed that "if a person has ALS, than he/she must be depressed and have a low quality of life"(Rabkin et al., 2009).

The reaction toward a grave diagnosis such as ALS will vary greatly from person to person. Individual's characteristics will lead to a personal reaction that may include depressive features, despair, hopelessness, but there remains potential for the individual to find hope, and maintain hope in the face of such serious prognosis (McDonald et al., 1994). Therefore, even if we can find out, statistically, the average score of each psychological issue involved, no aggregate research will be able to consider the whole complexity of the individual reaction.

The practice of clinical psychology use to be guided by an idiographic approach, with an attention to research results derived from a nomothetic point of view. However, in certain cases, prejudices for a clinical situation may interfere in the process of individual knowledge. In the ALS field, considering the low prevalence of the disease, it is possible that a professional without a good deal of knowledge about such illnesses may overestimate depressive features based on assumption. A similar concept is also important for other types or clinicians, such as the physicians, in particular when they are not used to treat a particular clinical situation.

One way of better understanding a patient's world is to complete a quality of life (QoL) questionnaire, though care should be taken when selecting a questionnaire for this purpose. QoL is defined by the World Health Organisation as a "broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs, and their relationship to salient features of their environment" (WHOQOL Group, 1998). There are two different conceptualizations of QoL, known as health-related Quality of Life (HRQoL), and subjective well-being (SWB). HRQoL largely quantifies QoL based patient self-reported symptoms and ability to carry out activities of daily living. Subjective well-being, otherwise known as "Individual Quality of Life" in ALS research literature (Clarke et al., 2001), refers to a positive state of mind and satisfaction with life in general, and is not contingent on assessment of symptom severity. According to the construct of HRQoL and the manner in which it conceptualizes QoL, patients with ALS *must* have a lower QoL than the general population, with further decreases as symptom severity increases, in line with disease progression. However, past research has shown that QoL is unrelated to physical strength and the functional capacity (Goldstein et al., 2002; Pagnini, 2012). Therefore, when administering a QoL measure, clinicians must be aware of the subtle, but very important distinction between QoL and the confusingly named

HRQoL. Ideally, clinicians should always administer questionnaires that have been shown to work well with the intended illness group. Even questionnaires that are apparently suitable and ostensibly avoid somatic symptoms of depression have been shown to overestimate depressive features for ALS patients (Gibbons et al., 2011).

Even if researchers may take advantages from standardized questions and replies, clinicians should also include a patient-based focus. In the assessment of the QoL, for example, there are many questionnaires that are useful to understand how a person feels, with different degrees of sensitivity. One of the most interesting instruments for the assessment of the individual needs, beliefs and emotions, is the Schedule for the Evaluation of Individual Quality of Life (SEIQoL) (Hickey et al., 1996) that asks people to indicate the five most relevant domains for their well-being, to rate them and to classify among each other. Even if the score obtained has been criticized (Felgoise et al., 2009) and has some limitations from the research point of view, the clinical process of domain selection and rating may provide interesting insights about the individual's situation and prove useful in the formulation process, coherently with a SWB approach. The use of a similar approach by clinical psychologists and physicians who work with chronic illnesses may allow assist in understand the patient's individual clinical issues, reducing prejudices and the risk of a blind application of a nomothetic approach.

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Attitudes toward assisted suicide and life-prolonging measures in Swiss ALS patients and their caregivers

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Objectives: In Switzerland, assisted suicide (AS) is legal, provided that the person seeking assistance has decisional capacity and the person assisting is not motivated by reasons of self-interest. However, in this particular setting nothing is known about patients' and their caregivers' attitudes toward AS and life-prolonging measures. **Methods:** Data was retrieved through validated questionnaires and personal interviews in 33 patients and their caregivers covering the following domains: physical function according to the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), demographic data, quality of life, anxiety, depression, social situation, spirituality, burden of disease, life-prolonging, and life-shortening acts. **Results:** In patients the median time after diagnosis was 9 months (2–90) and the median Amyotrophic Lateral Sclerosis (ALS) FRS-R score was 37 (22–48). The majority of patients (94%; $n = 31$) had no desire to hasten death. Patients' and caregivers' attitudes toward Percutaneous Endoscopic Gastrostomy (PEG) and Non-Invasive Ventilation (NIV) differed. Significantly more patients than caregivers (21.2 versus 3.1%) stated that they were against NIV ($p = 0.049$) and against PEG (27.3 versus 3.1%; $p = 0.031$). Answers regarding tracheotomy were not significantly different ($p = 0.139$). Caregivers scored significantly higher levels of "suffering" ($p = 0.007$), "loneliness" ($p = 0.006$), and "emotional distress" answering the questionnaires ($p < 0.001$). Suffering ($p < 0.026$) and loneliness ($p < 0.016$) were related to the score of the Hospital Anxiety and Depression Scale (HADS) in patients. **Conclusion:** A liberal legal setting does not necessarily promote the wish for AS. However, the desire to discuss AS is prevalent in ALS patients. There is a higher level of suffering and loneliness on the caregivers' side. A longitudinal study is warranted.

Keywords: ALS, motor neuron disease, quality of life, depression, end of life

INTRODUCTION

During the course of the disease, Amyotrophic Lateral Sclerosis (ALS) patients may suffer from depression, hopelessness, the feeling of loneliness, and loss of control (Rabkin et al., 2000, 2005; Albert et al., 2005; Olney and Lomen-Hoerth, 2005). In the terminal phase respiratory distress, anxiety, and other distressing symptoms may occur (Mandler et al., 2001). Given the suffering associated with the disease, some patients choose to decline life-prolonging measures such as Percutaneous Endoscopic Gastrostomy (PEG) and Non-Invasive Ventilation (NIV) and/or wish to hasten death (Ganzini et al., 1998; Veldink et al., 2002; Fang et al., 2008; Maessen et al., 2009). In an early study from Oregon, about 56% of all ALS patients considered physician-assisted suicide (PAS; legalized after 1997) during the terminal phase and 73% of caregivers and patients had similar attitudes toward PAS (Ganzini et al., 1998). In the Netherlands, during the 2000–2005 period 16.8% of ALS patients decided for euthanasia or PAS (Maessen et al., 2009), while in Sweden (where PAS is not legalized), ALS patients have a sixfold increased risk of committing suicide (Fang et al., 2008). Factors such as depression, hopelessness, loss of meaning, and purpose in life have been discussed to be associated with the wish to hasten death, whereas the contrary applies to religious faith and spiritual beliefs (Rabkin et al., 2000, 2005; Albert et al., 2005; Olney and Lomen-Hoerth, 2005). These findings are not consistent between different countries (Maessen et al., 2009). Moreover, there is a lack of longitudinal studies analyzing changes of these factors over time. It is also unclear whether the legal background in different countries influences patients' attitudes toward assisted suicide (AS) as comparative studies are lacking.

In Switzerland, however, assistance in committing suicide by a physician or a lay person is not explicitly regulated by law, but article 115 of the Swiss Penal Code allows assistance in suicide provided that the person seeking assistance has decisional capacity and the person assisting – physician or lay person – is not motivated by reasons of self-interest. Based on this article, Swiss "right to die" organizations offer assistance to commit suicide (Fischer et al., 2008). A recent study from the City of Zurich revealed that between 2001 and 2004 "Dignitas or Exit Deutsche Schweiz" had facilitated a total of 421 cases of AS (Fischer et al., 2008). Amongst the patients, 60% had been non-residents in Switzerland emphasizing the problem of "suicide tourism." Twenty-four percent of ASs were patients with "neurological disorders" including

ALS. However, no information is available about the total number of ALS patients, their motivation and associated factors that had made them choose this exit strategy.

The objective of this study is to analyze patients' and caregivers' attitudes toward AS, life-prolonging measures as well as associated factors (e.g., depression, quality of life (QoL), loneliness, suffering, education, profession, family status, living situation, Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS, and time after diagnosis) in a country with a comparatively easy access to AS.

METHODS AND PARTICIPANTS

PARTICIPANTS

Swiss patients and their primary caregivers were recruited from a tertiary referral center (Muskelzentrum/ALS clinic) at the Kantonsspital St. Gallen. Patients and caregivers attended the ALS outpatient clinic on a regular basis (usually every 3 months). Patients and caregivers had to be at least 18 years old. Further inclusion criteria for patients were a diagnosis of definitive, probable, or probable laboratory supported ALS according to the revised El Escorial Criteria (Brooks et al., 2000). Patients were only eligible if they had been informed about their ALS diagnosis, disease progression, prognosis, and therapeutic options including PEG insertion and different forms of ventilation (e.g., NIV, tracheotomy). The discussion about PEG and ventilation was usually triggered by clinical decline that resulted in use of PEG or NIV. Both issues are part of ALS – specific advanced directives which are routinely applied during this discussion (Benditt et al., 2001). Patients who inquired about these interventions shortly after diagnosis were also eligible. The study was approved by the local ethics committee and all patients and caregivers gave written informed consent.

For this study inclusion criteria, exclusion criteria, variables, and statistical analysis were pre-specified. Data were retrieved through questionnaires and personal interviews during home visits. The data collection took place as soon as patients had been informed about life-prolonging measures. Interviews were carried out by a researcher trained in interview technique, experienced in pastoral care, and medical ethics, not involved in clinical care of the patients and their primary caregivers. Patients and caregivers filled in the questionnaires simultaneously. In case the patient was unable to complete the questionnaire by his/her own hand due to weakness, the interviewer completed the questionnaire according to the patient's statements. The mean duration of the interview was approximately 60 min. After the interview, the primary caregiver/relative had the opportunity to clarify any issues that may have arisen during completion of the questionnaire. Specifically the following data and questionnaires were retrieved/applied:

Demographic data

The collection of data included age, sex, living situation, education, profession, and religious confession.

Numerical rating scale

(Eleven-point format; 0–10) asking the following questions: (1) What is your current QoL?; (2) How much are you suffering from your disease/from the disease of your partner?; (3) How lonely do you feel?; (4) How strong is your current desire to ask others for help to end your life prematurely?; (5) How distressing or how helpful was it for you to speak about such issues?

Hospital anxiety and depression scale (HADS)

A self-assessment scale to quantify patients' anxiety and depression by choosing one response from four given. The range is from 0 to 42 with the maximum score indicating a high level of depression and anxiety (Bjelland et al., 2002).

Questions regarding life-prolonging measures and hastening death

Patients' and caregivers' opinions were assessed with regards to tracheotomy, NIV, and PEG within a four-point response format. The following questions were asked: What is your attitude toward the following life-prolonging measures: (a) Tracheotomy; (b) NIV; (c) PEG? Possible answers to each item were: (a) I am not sure; (b) I am absolutely in favor of it; (c) I am in favor of it under certain circumstances; (d) I am against it.

Questions in yes/no format included: (1) Have you ever thought about committing suicide after receiving your diagnosis?; (2) Can you imagine a future scenario in which a physician prescribes a fatal drug which you administer yourself?; (3) Can you imagine a future scenario in which a physician prescribes and administers to you a fatal drug?; (4) Have you ever discussed suicide with others?; (5) Would you like to discuss suicide with a physician?

Idler index of religiosity (IRR)

The IRR assesses both public and private religiosity: (1) summing up attendance at religious meetings and services and the number of church members known to the patient; (2) self-assessment of personal religiosity as well as the amount of strength and comfort provided by personal faith (Robbins et al., 2001).

STATISTICAL ANALYSIS

For continuous variables (e.g., age) the mean of the differences between "patient" and "caregiver" was calculated by the t-test. Variables applying scores were compared by the Wilcoxon signed rank tests providing the median difference and its 95% confidence limits. Differences of ordered categorical variables (four-point response format) were tested by the Fishers exact test and the McNemar's Chi-squared test. For analyzing possible associations between the paired samples ("patient,""caregiver") the Spearman's rho correlation coefficient was applied. The level of significance was $p < 0.05$.

In order to predict score ratios between patients and caregiver, generalized linear mixed-effects models with group ("patient" and "caregiver") and given variables as fixed factors (sex, age, education, profession, family status, living situation, children, ALSFRS, time after diagnosis, and QoL) and subject ("patient") as random factor were performed either as multivariate or univariate model (for each parameter as a separate model). In order to predict dichotomous variables (yes versus no) concerning suicidal ideation for patients, logistic regression models were performed providing odds ratios (OR) and 95% confidence intervals (CI) with corresponding p-values.

All analyses were performed using R version 2.12.2 (R Development Core Team, 2011).

RESULTS

DEMOGRAPHIC DATA

During the recruitment period from 2008 to 2010 a total of 59 patients and caregivers were asked whether they would participate in this study. Twenty-six patients declined, 33 patients and their caregivers agreed to participate. The most frequent reason for declining participation was "no interest" and reluctance toward the themes of religiosity and spirituality. **Table 1** summarizes the epidemiological data, social status, and religious denominations of patients and their caregivers. Mean age of patients was 59.6 and mean age of caregivers was 56.9 (paired t-test; $p = 0{,}065$). The median time after diagnosis at which the first interview took place was 9 months (2–90) and the median ALSFRS-R was 37 (22–48).

ASSISTED SUICIDE/HASTENING DEATH

Thirteen patients (39%) answered that during the course of the disease they had thought about the possibility of committing suicide (**Table 2**). However, at the time of the interview, 31 of the patients (94%) expressed no wish to hasten death by AS. Thirty-three percent of the patients would like to discuss the issue "suicide" with a physician. Fifty-four percent of the patients could imagine asking a physician in the future to prescribe a fatal drug that they could take themselves; 57% could imagine a physician administer such a drug to them in the future. Logistic regression revealed that for patients QoL was the major predictor toward suicidal ideation (OR: 0.58, CI: 0.35–0.99) and the wish to discuss suicide with a physician (OR: 0.32, CI: 0.13–0.81, **Table 2**). The number of children (OR: 0.54, CI: 0.28–1.04) and HADS score (OR: 1.2, CI: 0.99–1.45) was also predictive of the wish to discuss suicide with a physician. Other analyzed factors (education, profession, family status, living situation, ALSFRS, and time after diagnosis) were not associated.

LIFE-PROLONGING MEASURES

The majority of patients (57.6%) and caregivers (50.0%) were against tracheotomy (**Table 3**). As verified by the McNemar test no significant difference was detected between the coincident answers of the two study groups ($p = 0.37$). No patient and no caregiver were generally in favor of its application, only "under certain circumstances" (27.3 patients versus 25.0% caregivers). The remaining interviewees were "unsure" about tracheotomy. Within the four-point response format attitudes between patients and caregivers regarding NIV and PEG differed (Fishers exact test). Significantly more patients than caregivers (21.2 versus 3.1%) stated that they were against NIV ($p = 0.049$) and against PEG (27.3 versus 3.1%; $p = 0.031$).

Table 1 | Demographic data.

	Patients % (*n*)	Caregivers % (*n*)
Age (mean, range)	59.6 (38–79)	56.9 (31–79)
Sex		
Female	36.4 (12)	62.5 (20)
Male	63.6 (21)	37.5 (12)
Living situation		
Alone	9.1 (3)	3.1 (1)
With spouse	57.6 (19)	59.4 (19)
With spouse and child(ren)	33.3 (11)	37.5 (12)
Religious confession		
Roman-catholic	51.5 (17)	46.9 (15)
Protestant	33.3 (11)	25.0 (8)
No confession	15.2 (5)	28.1 (9)

QUALITY OF LIFE AND BURDEN OF DISEASE

The median of QoL rated on a 11-point scale was six for patients and caregivers ($p = 0.68$). "Suffering," "loneliness," and "emotional distress answering the questionnaire" were significantly higher on the caregivers' than on the patients' side (**Table 4**). The mean HADS score of patients was 10.6 ± 5.1. Univariate analysis by a general linear mixed-effects model revealed a significant influence of the HADS on "suffering" (OR: 1.04 (95% CI: 1.01–1.07, $p = 0.027$) and "loneliness" (OR: 1.17 (95% CI: 1.04–1.33, $p = 0.017$) for coincident answers of patients and caregivers. Other analyzed factors (sex, age, education, profession, family status, living situation, children, ALSFRS-R, time after diagnosis, and QoL) did not show a significant effect, both in univariate and multivariate analysis (data not shown).

RELIGIOSITY

With regard to publicly practiced or private religiosity patients considered themselves to be more religious than their caregivers ($p < 0.001$) and derived more strength and comfort from their faith ($p < 0.01$).

DISCUSSION

The most important finding of the study is that at the time of the interview 94% of the patients had no intention to hasten death. This seems notable as the Swiss legal situation is liberal regarding assistance to commit suicide and the society is tolerating the practice of lay organizations offering the assistance through the collaboration of physicians and lay persons (van der Heide et al., 2003; Reiter-Theil, 2006). In contrast, a comparable study from Germany on ALS patients revealed that 37% of patients wished to hasten death (Jox et al., 2007). Germany is characterized by a liberal regulation of AS in penal law, but at the same time by a restrictive regulation and prohibition of PAS in the medical law (Reiter-Theil, 2006). The only difference between the Swiss and the German study methodology was that our patients were interviewed at home, whereas in the German study the interviews took place in the outpatient clinical. This difference, however, is unlikely to account for the imbalance and suggests that not the legal background as such (e.g., a more liberal legal situation promotes AS), but other factors must be responsible for the wish to hasten death. Previous studies from Oregon and the Netherlands where PAS is also legal, revealed a high prevalence of AS and euthanasia among ALS patients (Ganzini et al., 1998, 2002; Veldink et al., 2002; Albert et al., 2005; Maessen et al., 2009). This contrasts with our findings where only a minority of patients expressed a wish to hasten death. However, a comparison of our results with the Oregonian and Dutch studies is difficult as they were either retrospective (Veldink et al., 2002; Maessen et al., 2009) or interviews took place at a late to terminal stage (Ganzini et al., 2002; Albert et al., 2005). Longitudinal studies analyzing attitudes toward AS

Table 2 | Patient suicidality; n.s., no significant effect.

	Yes % (*n*)	No % (*n*)	No answer % (*n*)	Associated factors (adjusted for gender and age)
Thought about suicide after receiving diagnosis	39.4 (13)	60.6 (20)	0	n.s.
Can imagine future scenario: committing suicide by means of a prescribed drug	54.5 (18)	45.5 (15)	0	Quality of life ($p = 0.026$)
Can imagine future scenario: suicide with the help of physician administering fatal drug	57.6 (19)	42.4 (14)	0	n.s.
Have already discussed suicide with others	33.3 (11)	66.7 (22)	0	n.s.
Would like to discuss suicide with a physician	33.3 (11)	60.6 (20)	6.1 (2)	Number of children ($p = 0.048$), quality of life ($p < 0.001$), HADS ($p = 0.037$)

Table 3 | Live-prolonging measures: "what is your attitude toward the following life-prolonging measures?" *p*-values derived from McNemar test.

	Not sure% (*n*)	Absolutely yes % (*n*)	Yes under certain circumstances % (*n*)	Against % (*n*)	*p*
Tracheotomy					0.37
Patients	15.2 (5)	0	27.3 (9)	57.6 (19)	
Caregivers	25.0 (8)	0	25 (8)	50.0 (16)	
NIV					0.17
Patients	3.0 (1)	42.4 (14)	33.3 (11)	21.2 (7)	
Caregivers	18.8 (6)	43.8 (14)	34.4 (11)	3.1 (1)	
PEG					0.75
Patients	12.1 (4)	24.2 (8)	36.4 (12)	27.3 (9)	
Caregivers	25.0 (8)	18.8 (6)	53.1 (17)	3.1 (1)	

Table 4 | Quality of life and burden of disease variables rated on self-rating scales (0–10).

Parameters	Patients (median, IQR)	Caregivers (median, IQR)	Difference of medians	Lower 95% CI	Upper % 95 CI	*p*-value
Quality of life	6 (5–8)	6 (5–7)	0.25	−1.0	1.5	0.68
Loneliness	0 (0–1)	2 (0–6)	−3.25	−5.5	−1.5	0.003
Emotional distress	0 (0–1)	3 (0.8–5)	−4.25	−5.5	−3.0	<0.001
Suffering	5 (3–6)	6.5 (5–8)	−2.25	−3.5	−0.5	0.006

Differences determined by Wilcoxon signed rank test. IQR, inter quartile range.

have not been published yet, but are important to understand whether these attitudes depend on the degree of disability.

With respect to preferences for life-prolonging and ameliorative technologies it seems that ALS patients make choices consistent with preferences expressed shortly after diagnosis (Albert et al., 1999). It is unclear whether this also applies to attitudes toward AS. Nevertheless, more than one-third (39%) of our patients had thought about the possibility of committing suicide after being diagnosed with ALS and 33% of the patients expressed the wish to discuss suicide with their physician. Even 58% said they could imagine a future scenario in which a physician would not only prescribe, but also administer a fatal drug (i.e., euthanasia which is prohibited in Switzerland) to them. This mirrors other studies which have shown that the themes of assisted dying and suicide are prevalent in ALS patients (Ganzini et al., 1998, 2002; Albert et al., 2005; Palmieri et al., 2010). The wish of patients to discuss suicide with a physician was associated with poorer QoL and a higher HADS score. It can be concluded that medical caregivers need to develop an openness and willingness to discuss with and inform patients about suicide and to deal with the fact that a considerable number of patients facing end of life may ask for their physician's active involvement in hastening death (Bascom and Tolle, 2002; Jox et al., 2007; Moore et al., 2007; Oliver et al., 2007). The prevalence for a physician's active involvement in hastening death in the future corresponds with a retrospective study (Lofmark et al., 2008) which reports that 37% of the Swiss physicians ($n = 1397$) had received a patient request to hasten death.

Patients' and caregivers' attitudes regarding life-prolonging measures were largely concordant. Fifty-eight percent of patients and 50% of caregivers were against tracheotomy. However, caregivers (mean: 22.2%) in general were considerably more unsure about NIV, PEG, and tracheotomy than patients (mean: 9.8%). Furthermore significantly more patients than caregivers were strictly against PEG and NIV. This confirms a fundamental need for more information and discussion about life-prolonging measures as has also been

shown by other studies (Albert et al., 1999; Trail et al., 2003).

Another important finding of this study is that caregivers scored significantly higher in the domains of suffering, loneliness, and distress filling out the questionnaires compared to patients, despite overall QoL being not different between patients and their caregivers. The only associated factor was patients' depression and anxiety as measured by HADS. Sex, age, education, profession, family status, living situation, children, ALSFRS, time after diagnosis, and QoL were not related. Previous studies also revealed that depression in patients is associated with caregiver burden (Chio et al., 2005) and that patients' and caregivers' well-being are interrelated (Pagnini et al., 2011). Other examined factors such as time since diagnosis and degree of disability were not related in our as in previous studies (Rabkin et al., 2000; Chio et al., 2005). This is in contrast with studies that have shown that caregiver burden and distress are associated with the degree of disability (Hecht et al., 2003; Chio et al., 2005; Lo Coco et al., 2005). However, it needs to be taken into account that the patients in our study had only mild to moderate handicap as compared to other studies. A prospective longitudinal study may help to resolve this discrepancy and would also reveal dynamic changes as disease and disability progress.

This study has several limitations. Patients were recruited from a single center and may therefore not be representative for all Swiss ALS patients. At our ALS Clinic patient care is strictly adhering to international guidelines (Miller et al., 2009; Andersen et al., 2012) which may not be the case in all Swiss centers. Each follow-up consultation lasts 2 h allowing ample time to discuss end of life decisions and related issues that may have influenced the results. Second, since spirituality and religiosity were part of the study, this may have introduced a self-selection bias toward couples that tend to be more religious which is known to be inversely related to the wish to hasten death (Albert et al., 2005). The themes of religiosity/spirituality may also contribute for the relatively high non-participate rate of 44%. However, these problems are inherent in almost all of the published interview studies.

CONCLUSION

In summary the "liberal" Swiss legal setting does not promote the wish for AS, but the wish to discuss AS is prevalent amongst ALS patients even in moderately advanced stages of the disease. This wish is associated with poorer QoL and degree of depression.

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AUTHOR NOTE

This study was approved by the ethics committee of St. Gallen.

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Efficacy of hypnosis-based treatment in amyotrophic lateral sclerosis: a pilot study

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Background: Amyotrophic lateral sclerosis (ALS) and its devastating neurodegenerative consequences have an inevitably psychological impact on patients and their caregivers: however, although it would be strongly needed, there is a lack of research on the efficacy of psychological intervention. Our aim was to investigate the effect of hypnosis-based intervention on psychological and perceived physical wellbeing in patients and the indirect effect on caregivers. **Methods:** We recruited eight ALS volunteers patients as a pilot sample for an hypnosis intervention and self-hypnosis training protocol lasting 1 month. Anxiety and depression level was measured in patients and caregivers at pre and post treatment phase. Quality of life and perceived physical symptoms changes were also investigated in patients. **Results:** One month pre-post treatment improvement in depression, anxiety, and quality of life was clearly clinically observed and confirmed by psychometric analyses on questionnaire data. Moreover, decreases in physical symptoms such as pain, sleep disorders, emotional lability, and fasciculations were reported by our patients. Improvements in caregiver psychological wellbeing, likely as a consequence of patients psychological and perceived physical symptomatology improvement, were also observed. **Conclusion:** To the best of our knowledge, even if at a preliminary level, this is the first report on efficacy psychological intervention protocol on ALS patients. The findings provide initial support for using hypnosis and self-hypnosis training to manage some ALS physical consequences and mainly to cope its dramatic psychological implications for patients and, indirectly, for their caregivers.

Keywords: amyotrophic lateral sclerosis, hypnotherapy, self-hypnosis, psychological intervention

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is classically characterized by progressive loss of upper and lower motor neurons, causing weakness and hypotrophy of upper and lower limbs, dysphagia and dysarthria, and respiratory failure, which is the most common cause of death. Frequently, patients require intubation and mechanical ventilation and, in a large proportion, receive tracheostomy, leading to inevitably, overwhelming locked-in syndrome (Vianello et al., 2011). Secondary symptoms that affects patient quality of life are also pain (Pagnini et al., 2011a; Chiò et al., 2012; Pagnini, 2012), sleep disorders (Blackhall, 2012), emotional lability (Palmieri et al., 2009), and fasciculations (Rana et al., 2009; De Carvalho and Swash, 2012). Although pharmacology and physiotherapy research efforts, effective treatments for ALS have remained elusive (Beghi et al., 2011). Not surprisingly, a very active community of researchers is dedicated to deepen the devastating psychological impact of ALS in patients and caregivers. Depression and anxiety are two reactions typically described in response of the disease, mainly in the first stage, in which are accompanied by anger, hopelessness, and suicidal ideation (Palmieri et al., 2010a; Pagnini, 2012). Patient psychic status has been found directly related to caregiver's one (Palmieri et al., 2009; Pagnini et al., 2010a, 2011b). Analogously, caregiver psychological status has a deep impact on patient (Chiò et al., 2005). Although psychological wellbeing is crucial also in determining a better prognosis in ALS (McDonald et al., 1994), there is an absence of research on efficacy of psychological intervention in ALS. That is what was recently highlighted by Pagnini et al. (2012), in a relevant short communication published in ALS leading journal, eloquently entitled: "ALS: time for research on psychological intervention?" The communication arises the importance to carry out exploratory investigation on the impact and the suitability of psychological treatments for ALS patients. Given the devastating physical involvement of the disease, which affects also speech ability and eventually may result in the locked-in syndrome, a mind-body treatment technique, such as hypnosis, mindfulness meditation, or biofeedback (techniques included among complementary therapies in neurology; Wahbeh et al., 2008), could represent the eligible psychological forms of intervention. In particular, probably no other contemporary therapeutic intervention has a longer and corroborated clinical/scientific history than that of hypnosis. Our purpose was to explore, in the form of a pilot study, the applicability and efficacy of a hypnosis-based treatment in a small sample of ALS patients. Since the potential treatment

benefit obtained from individual active participation (Bandura, 1997), a self-hypnosis training, other than ericksonian hypnosis classical intervention, was proposed to patients. Our primary hypothesis was that the treatment and the training may determine relevant reductions in the two primary psychological reactions to the disease, i.e., anxiety and depression, and, in general, in quality of life. In addition, we aimed to explore if the participation to the hypnosis training could produce significant improvements in the perception of the above-mentioned physical secondary symptomatology (i.e., pain, sleep disorders, emotional lability, and fasciculations). Finally, we hypothesized an eventual reduction of caregivers' anxiety and depression, as indirect consequence of patients psychological improvement.

MATERIALS AND METHODS

PARTICIPANTS AND PROCEDURE

Eight consecutive patients with a diagnosis of probable or definite ALS (in accordance with the Revised El Escorial Criteria; Brooks et al., 2000) presenting to the Motor Neuron Disease Center of Padova University Hospital and their respective caregivers (seven spouses, one daughter) were recruited as volunteers for the pilot study. Patients underwent complete neurological and neuropsychological examination within a week before the first treatment session. Our sample was composed by four males and four females, with mean age of 55 years (SD = 7.14); ALSFRS-r (Cedarbaum et al., 1999) mean score was 35 (SD = 7.1), ranging from 21 to 42; four had bulbar onset, and one of them was completely enable to speak; two were completely enable to move upper limbs. Patient neuropsychological profiles did not revealed any alteration if compared to normative data. Further demographic and clinical characteristics of participants are reported in **Table 1**. The intervention protocol consisted of four weekly domiciliary sessions of hypnosis-based intervention, administered by a psychologist extensively trained in ericksonian hypnotic method and analgesic hypnosis. All sessions were based on a standardized, general induction followed by individual suggestion modified for the patient according to his/her psychological status and physical symptoms. Hypnotic suggestions were constituted by guided visual imagery oriented with an emphasis on developing physical symptomatology controls, such as muscle pain or emotional lability, sense of resilience, self-consciousness, and illness acceptance. After the hypnosis session, which lasted about 45 min, patient was supported by the aiding of the hypnotherapist to try again in recreating hypnotic status with self-hypnosis technique. The general induction, common for all treatment phases and for all patients, was recorded in a CD audio and was left to each patient who was encouraged to practice at least one time every day. Such procedure is inspired by Jensen et al. (2009, 2011) hypnosis-based protocol, successfully applied on multiple sclerosis patients. Sessions included also a brief clinical interview with patient and/or caregiver (separately) collected by a psychotherapist with 10-years experience with ALS. The interview aimed to investigate the subjective perception of the hypnosis treatment efficacy both on psychological and physical perspective, the frequency of application and the eventual difficulties. Each entirely domiciliary session lasted about 2 h. Immediately before the first and after the last treatment, patients and caregivers psychological variables were collected by means of standardized, Italian-validated *ad hoc* questionnaires, as described in the next paragraph. Patient impressions on physical symptomatology were also systematically recorded. The study protocol was approved by the Ethical Committee of the University of Padova and carried out in accordance with the principles of the Declaration Helsinki as revised in 1983. All the participants signed a consent statement after being informed about the study's purpose and methods.

MEASURES

The Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983), a measure largely used to identify caseness of anxiety disorders and depression among non-psychiatric patients (Bjelland et al., 2002), easy to administer and well accepted, was employed for patients and their caregivers. It is divided into an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D) both containing seven intermingled items on a 4-point Likert scale (ranging 0–3).

Patients also underwent the Amyotrophic Lateral Sclerosis Specific Quality of Life – revised (ALSSQOL-r; Simmons et al., 2006; Pagnini et al., 2010b), a 46-items on a 11-point Likert scale (ranging 0–10) derived from interviews with ALS patients. The ALSSQOL-r is composed by six subscale including negative

Table 1 | Participants demographic and clinical characteristics.

Patient	Age	Gender	Time since diagnosis (months)	Onset	ALSFRS-r	FVC (%)	Caregivers age (years); gender
I	64	*F*	24	Bulbar	42	82	(32); *F**
II	55	*M*	15	Limb	38	82	(50); *F*
III	59	*F*	10	Limb	40	86	(57); *M*
IV	54	*M*	26	Limb	21	56	(50); *F*
V	43	*M*	18	Limb	39	92	(40); *F*
VI	53	*M*	40	Limb	30	75	(53); *F*
VII	55	*F*	24	Bulbar	39	91	(56); *M*
VIII	66	*F*	10	Limb	31	72	(69); *M*

ALS-FRS-r, amyotrophic lateral sclerosis functional rating scale-revised; FVC, forced vital capacity.

**Daughter; in the other cases, caregiver was the spouse.*

emotion (13 items), interaction with people and their environment (11 items), intimacy (seven items), religiousness and spirituality (four items), physical symptoms (six items), and bulbar functioning (five-items).

The five-items ALS Assessment Questionnaire (ALSAQ-5), a further, brief specific quality of life measure derived from the broader ALSAQ-40 (Jenkinson and Fitzpatrick, 2001; Palmieri et al., 2010b), was also administered to patients. Items are composed on a five-point Likert scale (ranging 1–5). Such measure was introduced, in addition to the more exhaustive, even if different in content, ALSSQOL-r, in the perspective of eventual 3 and 6 months follow-up, in order to obviate eventual drop out in quality of life measurement (such phenomenon could be due to progressive physical impairment that can frustrate responding questionnaire with many items).

Global satisfaction with hypnotic-based intervention score in terms of perceived efficacy was assessed asking patients to rate, after treatment, how satisfied they were with the treatment they received on a 1–5 Likert scale (from one as totally unsatisfied to five as extremely satisfied). Subjective perception of secondary symptoms affecting patient everyday life that could receive benefit from hypnosis-based treatment, namely pain, sleep disorders, emotional lability, and fasciculations, were qualitatively investigated before and after the treatment (for an example, in the time lapse immediately preceding the beginning of the treatment were asked to the patients: "Did you suffer physical pain (e.g., cramps)?" And, if yes, after the treatment was asked them: "Did you notice any improvement during the training period?"). To not overfatigue the patients with wide many items standardized measurements, we opted, at this preliminary level, to investigate such physical perceived changes with a simple open-answers interview, avoiding dimension-specific questionnaires for peculiar physical dysfunctions. Due to severity of motor impairment, not every patient would be able to fulfill self-report questionnaires responses. Therefore, to obviate eventual heterogeneity in the data collection, a trained psychologist administered all questionnaires in an eterodirected way.

DATA ANALYSIS

Pre-post differences in scores for each subscale of the questionnaires (HADS, ALSSQOL, ALSAQ-5) were analyzed for significance through Wilcoxon Signed Rank Tests at the 0.05 level, and the Cliff's delta (∂) statistic was used to assess effect size. Cliff's delta (Cliff, 1993) was chosen as a more robust alternative to the common Cohen's d in conditions were non-parametric statistics are advisable, such as small sample sizes where it is not safe to assume a normal distribution (Hess and Kromrey, 2004). An high effect size is considered $\partial \geq |0{,}474|$, a medium effect size is $\partial = |0{,}33|$ and a low effect size is $\partial < |0{,}147|$ (Cohen, 1988). Analysis were performed with R software, version 2.15.1.

RESULTS

Patients declared to have successfully practiced self-hypnosis at least once every day in the great majority of the days during month treatment. The HADS scores showed that before the treatment two out of eight patients suffered from "mild" depression while the remaining six fell in the normality range; after the treatment all eight patients fell in the normality range for depression. Before the treatment, three patients out of eight suffered from "mild" anxiety, one suffered from "severe" anxiety, and the remaining four patients fell into the normality range. After the treatment, two out of eight patients suffered from "mild" anxiety while the six remaining had a normal score (of note, one was previously ranged as "moderate" and one was previously ranged as "severe"). Pre and post analysis of the HADS scores showed significant reduction in the anxiety subscale, with very high effect sizes (where an high effect size is considered $\partial \geq |0{,}474|$) both for patients ($W = 36$, $p = 0.008$; $\partial = -1$) and caregivers ($W = 21$, $p = 0.031$; $\partial = -0.75$); moreover, the HADS depression subscale showed a significant reduction in score with high effect size ($W = 28$, $p = 0.016$; $\partial = -0.875$) for the patients group only. Significant pre-post differences were also observed in the ALSSQOL-r average total score ($W = 1$, $p = 0.016$; $\partial = 0.75$), negative emotion subscale ($W = 0$, $p = 0.008$; $\partial = 1$), and religiosity/spirituality subscale ($W = 1$, $p = 0.031$; $\partial = 0.625$). The interaction ($W = 5$, $p = 0.078$; $\partial = 0.75$) and physical symptoms ($W = 0$, $p = 0.125$; $\partial = 0.75$) subscales' pre-post differences were not found significant, but still showed a large effect size, whereas the bulbar and intimacy subscales showed only a medium to small effect size. ALSAQ-5 questionnaire did not show any significant difference before and after the treatment ($W = 16$, $p = 0.219$; $\partial = 0.25$). Patient and caregiver questionnaires mean and standard deviation score, and pre to post treatment comparison in terms of statistical indices are shown in **Table 2**.

Regarding physical symptoms, both the two patients who were suffering from sleep disorders, four out of seven patients suffering from muscular pain and cramps, four out of five patients who were suffering fasciculations and each of the four patients suffering from emotional lability declared that their symptoms improved during the training period. A question on the perceived usefulness of the training, ranging from 0: "not useful at all" to 5: "very useful," showed an average score of 4.25 (SD = 0.71).

DISCUSSION

In contrast with the prolific scientific literature addressed to investigate the psychological impact of ALS on affected patients (Felgoise et al., 2010; Palmieri et al., 2010a; Lulé et al., 2012; Pagnini, 2012), the need to outline research on efficacy of psychological intervention has recently emerged (Pagnini et al., 2012). The current pilot study represents a preliminary response to such a relevant issue. Our psychological treatment, on a small patient sample size, was focused on hypnosis-based domiciliary intervention (hypnosis intervention and self-hypnosis training) and was designed to address three related goals: to assess the effect of such intervention on both reducing psychological suffering in ALS patients and giving relief from physical symptoms of the disease and consequently contributing to a positive psychological impact on caregivers. Our findings provided a clearly encouraging, although initial, support for using hypnosis to manage psychological and some physical consequences of ALS. In particular, results showed ALS patient improvements in depressive, anxiety symptomatology, and in general quality of life after 1 month treatment. Moreover, relevant pre to post treatment improvements in pain, disorders, emotional lability, and fasciculations were reported and

Table 2 | Patient pre and post treatment psychological measures.

Patient outcome variables (questionnaire scores)	Pre treatment mean (SD)	Post treatment mean (SD)	*P* (Wilcoxon W index)	Pre-post effect size (Cliff's delta)
HADS anxiety	8.12 (4.58)	4.5 (4.44)	**0.008**** (36)	−1
HADS depression	4.87 (2)	3 (2.33)	**0.016*** (28)	−0.87
ALSSAQOL-r negative emotions	7.38 (1.21)	8.44 (0.60)	**0.008**** (0)	−1
ALSSAQOL-r interaction	7.49 (1.21)	8.21 (1.17)	0.078 (5)	0.75
ALSSAQOL-r intimacy	6.21 (2.17)	6.28 (2.25)	0.437 (6.5)	0.25
ALSSAQOL-r religiousness	8.10 (2.34)	7.12 (1.76)	**0.031*** (1)	0.62
ALSSAQOL-r physical symptoms	7.06 (1.96)	7.71 (1.53)	0.125 (0)	0.75
ALSSAQOL-r bulbar functioning	6.82 (0.96)	6.95 (1.01)	0.250 (2)	0.37
ALSSAQOL-r total score	6.95 (0.99)	7.68 (0.89)	**0.016*** (1)	0.75
ALSAQ-5	45 (17.52)	41.87 (20.86)	0.219 (16)	0.25
CAREGIVER OUTCOME VARIABLES (QUESTIONNAIRE SCORES)				
HADS anxiety	8 (4.66)	6.12 (3.88)	**0.031*** (21)	−0.75
HADS depression	4.62 (4.78)	3.25 (5.33)	0.22 (22)	−0.37

HADS, hospital anxiety and depression scale; ALSSQOL-r, amyotrophic lateral sclerosis specific quality of life – revised; ALSAQ-5, 5-items amyotrophic lateral sclerosis assessment questionnaire.

*Significant results are in bold; *$p < 0.05$; **$p < 0.01$.*

attributed by patients to hypnosis-based intervention and self-hypnosis training. A satisfaction level from good to extreme was finally reported by patients involved in our study, confirming the appreciation and the applicability of the treatment. Caregiver depression and anxiety levels were observed to decrease during 1 month patient treatment, and such positive trend was attributed by them to patient gained psychological wellbeing.

Before the beginning of the treatment, two of our patients were classified as affected by "mild" depression and half of them as affected by "mild" to "severe" level of anxiety. Moreover, at the end of the treatment, the great majority of patients qualitatively showed, from a clinical point of view, a clear amelioration in such aspects, and the global psychometric analyses, calculated on HADS questionnaire scores, confirmed such clinical evidence. These findings on patient psychopathological remission, even if should be considered with caution at this preliminary stage of investigation, are undoubtedly of great interest for clinicians. As an example, depression and anxiety appear to be strongly related in the disease: Atassi et al. (2011) found that anxiety level resulted the unique ALS related symptom that can predict the occurrence of depression. Prevalence of depression in ALS has been reported as highly variable, depending by specific interview methods and assessment tools of investigation (Taylor et al., 2010), and could reach levels as high as 75% (Wicks et al., 2007). The nature of the wide difference in estimation of mood states in ALS is conceivably due also by the fact that the existential despair some patient feel in the face of their illness may be poorly described by the word of "depression." Their experience of overwhelming sense of demoralization, hopelessness, anger, and loss of meaning in the face of their mortality is something different of feel just depressed (Blackhall, 2012).

Our study highlighted also positive psychological changes in patients' quality of life after the training. Both specific ALS measures of the quality of life employed in the study, namely the ALSSAQOL (Simmons et al., 2006) and the ALSAQ-5 (Jenkinson and Fitzpatrick, 2001; Palmieri et al., 2010b), showed a clear improvement when comparing pre to post treatment mean scores. In particular, the ALSSAQOL "negative emotion" and "spiritually/religiousness" subscales reached the psychometric significance in terms of pre to post treatment improvements, while "interaction" and "physical symptoms" subscales appeared to be marginally significant. In the palliative care field, improving or maintain global quality of life is considered the crucial challenge in patients whose disease is not responsive to curative treatment as ALS. World Health Organization (WHO) scientific panel clearly established that the main objective of palliative care is achievement of the best quality of life for patients and their families until death (Doyle et al., 2003).

Interestingly, qualitative positive results have been emerged also in the disease secondary symptomatology, as it is perceived by patients. All of them declared to have perceived an improvement, from mild to extreme depending on cases, in pain, sleep disorders emotional lability, or fasciculation syndrome, whereas there was an occurrence before treatment. Since ALS devastating impact on motor system and dysphagic/dysartric, respiratory dysfunctioning, the impression is that secondary symptoms patient suffering have been underestimated by scientific attentional focus. However, recent clinical/epidemiological investigation highlighted such relevant disease consequences for patients. In particular, Chiò et al. (2012), in a wide epidemiological study, show that pain (e.g., muscle spasms, contractures, spasticity, abnormal stresses on the musculoskeletal system imposed by weak musculature) is frequent in all stages of ALS, but it often goes underrecognized and undertreated, recommending research efforts toward the appropriate ALS pain treatment. Our intervention protocol could be interpreted as addressed in such direction as well. The arena in which the hypnosis has probably proved its efficacy most adequately is, indeed, that of hypnotically induced analgesia, providing reduction of both chronic (e.g., cancer) and acute (e.g., painful medical procedure) pain (Freeman et al., 1999). As for ALS sleep disorders (resulting from factors such as reduced mobility,

muscle cramps and anxiety, restless legs, and increased myoclonic activity), it may produce daytime symptoms and impairment activities of daily living and can be further affected by an increased incidence of depression (Hetta and Jansson, 1997). In emotional lability and fasciculation syndrome, respectively underestimated source of deep embarrassment (Palmieri et al., 2009) and physical discomfort (Rana et al., 2009), as well for pain and sleep disorders, seems to play a psychological etiopathogenetic non-neglectable role (Palmieri et al., 2009; Rana et al., 2009). As a final confirmation of the treatment approval, in the overall judgment of satisfaction we asked to the patients, all of them declared a good from extreme satisfaction.

Relevant improvement in terms of depression and anxiety reduction, measured with the same patient assessment tools, was reported by caregivers. When asked, the great majority of them stated they were satisfied of hypnotic treatment and self-hypnosis training patient positive outcome, and that the improvement on patient psychological functioning, according to them, has lead to a probable effect on their own mood tone as well. The impact of patient suffering on family caregivers is a further understudied but important topic. Associations of patient distress with caregiver negative affect has recently been shown by some authors (Chiò et al., 2005; Gauthier et al., 2007; Boerner and Mock, 2012). On the other hand, patient's loss of physical functions was positively related with caregiver burden, anxiety, and somatic expression of depression (Pagnini et al., 2010a).

Our findings on treatment efficacy, in their globality, could appear surprising, but it should be mentioned the number of Authors who have recently enhanced the potentiality of hypnosis-based treatment, and, in general, mind-body techniques, leading to a rapid improvement on anxiety, and depression especially when they are reactive to a medical condition (Shih et al., 2009; Willemsen et al., 2010; Plaskota et al., 2012). Specifically, in the realm of neurological disorders, hypnosis has been reported as an effective adjunctive treatment for organic brain damage (Sullivan et al., 1974), Parkinson disease (Wain et al., 1990), stroke (Holroyd and Hill, 1989), peripheral nerve lesions (Pajntar et al., 1980), cases of organic paralysis (Lucas et al., 1981), various type of dystonia (De Benedittis, 1996), multiple sclerosis (Jensen et al., 2009, 2011), migraine (Ezra et al., 2012), and fibromialgy (Bernardy et al., 2011).

Although our results show promising and exciting insights, the study suffers of a number of limitations, including the typical ones that naturally characterize pilot studies. Primary among them, the small sample size have limited our ability to detect whole treatment effect from a psychometric point of view. A further criticism is the lack of a different treatment condition (e.g., a different mind-body intervention or psychopharmacological treatment) that controls for the effects of time, placebo condition, and expectancy effect. Lastly, additional measurement at pre treatment level in order to investigate psychological traits such as personality profile, attachment style and hypnotic absorption, dissociation, and suggestion ability could have been undoubtedly important variables to be compared with the treatment efficacy (Primavera and Patterson, 1991). Moreover it will be relevant to consider the frequency of self-hypnosis and verify its role in the efficacy of this kind of treatment with ALS patients.

In conclusion, our general aim was to lay some foundations to develop, in a future perspective, a protocol of eligible psychological interventions for ALS, "useful for a meaningful improvement in quality of life or reduction in psychological distress in patients and their caregivers" (Pagnini et al., 2012) and suitable to be proposed to patients with a such peculiar condition, involving bulbar dysfunctions and that can eventually lead to a locked-in syndrome. Despite the pilot study limitations, the findings provide clear support for the potential efficacy of hypnosis-based intervention to cope with devastating consequences of ALS. Further longitudinal researches using larger sample to help determine the reliability of the current findings are warranted.

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Resentment, hate, and hope in amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a fatal and progressive neurodegenerative disease. Despite much research having been conducted about psychological issues involved in living with ALS, anger, and resentment have yet to be investigated. Moreover, the construct of "hope" has received little attention, so far. An online survey was created to investigate hate, resentment, and hope issues in people with ALS, in relation to the willingness to adopt a strict nutrient-dense diet if it were shown to increase longevity. Results indicate that there is a high level of hope in the sample. People who have lived with ALS for more time expressed a higher level of hope to live 10 years or more. Those who are married were more likely to have hope of living 10 years or longer and more likely to have lower levels of hate against ALS. Dietary self-care choices appear to be related to hope issues. Resentment and hate tended to be higher in people who have had ALS for less time, and in women. Despite some methodological limitations, the results suggest that hope, hate, and resentment could be important issues to explore in future studies.

Keywords: anger, resentment, hope, amyotrophic lateral sclerosis, quality of life, caregivers, ALS, will to live

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal and progressive neurodegenerative disease, which affects motor neurons in the anterior horn of the spinal cord, the brainstem, and the motor cortex. It is a rare disease, with an incidence of 1.89 per 100,000/year in western countries (Worms, 2001). People with ALS experience a progressive muscle weakness, becoming relentlessly immobile, developing impaired speech, and respiration problems. In the late stages of the disease, progressing paralysis can result in a "locked-in" state in which only residual muscular movement is possible.

Despite the average life expectancy of about 3 years after symptom onset (Ilzecka et al., 2003), the progression of the disease is unpredictable, with 10% of patients with ALS living more than 10 years (Andrews, 2009). So far, research has not demonstrated that it is possible to stop the progression of the disease. Therefore, the improvement of patients' quality of life is often considered one of the primary goals of clinical management (Simmons, 2005; Pagnini, 2012).

Many psychological issues have been investigated in ALS, including psychological well-being, anxiety, and depression (Pagnini et al., 2012a), pain (Brettschneider et al., 2008), hopelessness (Plahuta et al., 2002), spiritual and existential well-being (Dal Bello-Haas et al., 2000). However, no study to our knowledge has investigated the topics of hate and resentment. Moreover, despite its clinical importance (Fanos et al., 2008), the issue of hope has received little empirical investigation. To date, no study has investigated the relationship among hate, resentment, and hope and their development through time.

Hate and resentment, as well as hope, are often reported as a psychological response toward a chronic and non-treatable illness. Clinical practice (Radunovic et al., 2007), as well as patients' perspectives (Melazzini, 2007), often report of anger reactions, expressed in various ways by the patient. Not surprisingly, a study by Palmieri et al. (2010) observed high levels of anger in the considered ALS population. The "relationship" established with the disease seems to change over time (De Groot et al., 2007), probably because of the advancement of the disease and/or a grief elaboration process. Clinical practice suggests that ALS is often the target of hate by the people who have it; resentment is another emotion expressed by the patients, as well as by their caregivers, but there are very few scientific data pertaining to those reactions.

The diagnosis of ALS may threaten hope, especially with the belief that there is nothing that can be done to change a patient's fate. However, many clinicians suggest that "hope" is a very important issue for the psychological well-being of patients and their caregivers (Centers, 2001). In the ALS scientific literature, the concept of "hope" is less investigated than the one of "hopelessness" (Plahuta et al., 2002). Hopelessness is related to depressive features, and with low levels of quality of life (Ganzini et al., 1999); moreover, hopelessness seems to predict the desire for assisted suicide (Ganzini et al., 2002).

Our rationale in this study was to investigate the prevalence and degree of hate and resentment in a sample of the ALS population, and to understand their relationships with time since diagnosis, hope, marital status, and other demographic characteristics. A further innovation of this research is the examination of these three variables in relationship to the willingness to extend one's longevity through nutritional self-care. This variable was included,

because clinical considerations made by Oster (the manuscript's first author, who is an 18 years ALS survivor) suggest that some people with ALS would not be willing to adopt a healthier diet even if it were to be shown to extend life. We wanted to investigate the prevalence of this mindset in our study's subject population, and to discover whether the variables of hate, resentment, and hope were related to this attitude.

MATERIALS AND METHODS

An online questionnaire was created with a Google spreadsheet, as part of a larger study. The overall survey was composed by 65 items, with both opened-ended and closed-ended questions; in case of closed-ended questions, subjects could choose among different sentences. The time requested to complete the entire survey ranged between 10 and 20 min. The survey was created with Google Documents tool and was accessible by subjects through a dedicated template. All the items were generated *ex novo* (therefore no cut-off-points could be expected). There were no forced answers. For the purpose of this study, we only used a selected sub-sample of items.

People with ALS were invited with messages that were posted in ALS forums, facebook, and a newsletter, as well as with an announcement on "The Healers" website. The purpose of the survey was described before subjects were asked to complete the questionnaire, stating that results would be analyzed only for research purposes, and there was no possibility to link the published data to their true identity.

Together with demographical data, subjects were asked to provide answers about hate, resentment, and hope, with questions like "Do you believe that there will be a cure for ALS in your lifetime?" and "What statement best describes the level of resentment that you feel about living with ALS?" Multiple answers were possible.

The analyses, both descriptive and inferential, were, carried out with Excel and SPSS software, are mainly descriptive statistics and cross-tabs analysis, using the Pearson's chi-squared test.

RESULTS

A total of 83 subjects with ALS completed the survey. The sample's characteristics are reported in **Table 1**. Missing values were excluded.

The answers provided to the questions are presented in the **Figures 1–5**.

People who answered positively to the question about the hope to live more than 10 years had a lower frequency of resentment, $\chi^2\ (6, N = 82) = 11.14, p < 0.05$, and hate $\chi^2\ (6, N = 81) = 13.48$, $p < 0.05$, toward the illness.

The level of resentment of ALS reported by subjects is highly related to the level of resentment perceived in the caregiver, $\chi^2\ (6, N = 81) = 41.09, p < 0.001$, and the level of hate toward ALS, $\chi^2\ (6, N = 81) = 58.21, p < 0.001$. The caregiver's resentment perceived by the patient is also related to the level of hate expressed by the subject, $\chi^2\ (6, N = 80) = 21.19, p < 0.05$. It seems that there is a tendency for a positive correlation among these three variables.

Subjects who have the hope to live 10 or more years would be more willing to follow a strict diet if it would increase the life expectancy by 1 year $\chi^2\ (6, N = 75) = 21.93, p < 0.01$, but no differences were found about the willingness to take a new drug with uncomfortable side effects. Both the questions about "hope" presented no differences with regards to the demographic variables.

Women report higher level of resentment, with higher frequencies of moderate/strong resentment answers, in comparison with males $\chi^2\ (3, N = 81) = 6.44, p < 0.05$. There is a similar tendency, non-significant ($p < 0.1$), with women reporting a higher hate level. Splitting the sample into two groups, using the median of the time since diagnosis, subjects who have had the disease for less time present with higher level of resentment $\chi^2\ (3, N = 81) = 8.05$, $p < 0.05$, and hate $\chi^2\ (3, N = 82) = 9.89, p < 0.05$.

The subjects who report a higher level of caregiver's resentment indicate with greater frequency the answer "yes" to the question "Do you believe that there is a relation between your dietary habits and the losses that you have experienced subsequent to ALS?" $\chi^2\ (9, N = 78) = 20.32, p < 0.05$.

Regarding hope, people who do not believe that there will be a cure for ALS in their lifetime were more likely to believe that they will not live for 10 years, compared to those who have the hope that a cure will be found $\chi^2\ (1, N = 78) = 4.67, p < 0.05$. People who answered "yes" to both the hope questions ($N = 21$), compared to those who answered "no" ($N = 11$), had ALS for a longer time (but without statistical differences), were more likely to be married $\chi^2\ (5, N = 32) = 13.38, p < 0.05$ and reported a lower level of hate against ALS $\chi^2\ (4, N = 32) = 8.06, p < 0.05$.

Considering the resentment level expressed by the subjects, in comparison with the resentment level that the subjects reported to be experienced by the caregivers, about half of the subjects (51.2%) express an equal level of resentment, the 21.3% report higher level of resentment experienced by the patient, while the 27.5% indicate the contrary. No differences arose about demographics or hope levels reported (all Chi Squares without significant results).

DISCUSSION

The present study from an online survey completed by men and women with ALS and analyzed with cross-sectional analyses – aimed to investigate levels of hate, resentment, and hope, and the relationships among them. These variables were also examined in relationship to the willingness to extend longevity through a commitment to disciplined nutritional self-care. To our knowledge, this is one of the first attempts to investigate, with a survey methodology, the point of view of people with ALS about the hope for longevity and a cure, and the level of hate and resentment toward the illness. Furthermore, we are not aware of any study examining motivation regarding nutritional self-care, related to the will to live.

In our sample, most of the subjects (70%) hoped to be able to live more than 10 years. The hope for a cure was somewhat less present. A third of the people who reported hope of seeing a cure in their lifetime, and more than half of the sample who reported not believing that they will have the chance to see a cure. These two issues were correlated. Interestingly, people in a marriage were more likely to have hope of living 10 years or longer and more likely to have lower levels of hate against ALS.

To hate ALS involves hating having ALS and all of the potentially frustrating and otherwise emotionally challenging experiences that occur in the lives of people with ALS, as well as hating the

Table 1 | Sample characteristics ($N = 83$).

		Frequency	%
Months since diagnosis [*M*, (SD)]	44.12 (84.32)		
Sex	Female	41	50
	Male	41	50
Marital status	Now married	56	68.3
	Widowed	4	4.9
	Divorced	11	13.4
	Separated	3	3.7
	Never married	3	3.7
	other	5	6.1
Highest degree	Less than high school	1	1.2
	High school graduate	18	22.2
	Some college credit	15	18.5
	Associate degree (e.g., AA, AS)	5	6.2
	Bachelor's degree (e.g., BA, AB, BS)	23	28.4
	Master's degree (e.g., MA, MS, MEng, MEd, MSW, MBA)	12	14.8
	Professional degree (e.g., MD, DDS, DVM, LLB, JD)	4	4.9
	Doctorate degree (e.g., PhD, EdD)	2	2.5
	other	1	1.2
Work activity	Employed for wages	13	15.9
	Self-employed	4	4.9
	Unemployed	12	14.6
	Retired	39	47.6
	Unable to work	13	15.9
	Other	1	1.2
Race	Asian	1	1.2
	Black or African American	1	1.2
	White	76	92.7
	Hispanic	4	4.9
Country/province	USA	73	89
	South America	1	1.2
	Europe	5	6.1
	Australia	1	1.2
	Canada	1	1.2
	Mexico	1	1.2
Life environment	City	28	34.1
	Country/Rural	10	12.2
	Suburban	28	34.1
	Small town	15	18.3
	Other	1	1.2

way one's own physiology is performing. Perhaps, our finding regarding marriage and hope suggests that people in marriages may build a vision of hope together, and that the meaning of their shared marital commitment could be protective against what is involved in hating one's life with ALS. Research into this area could give clinicians greater understanding of strategies that could facilitate greater hope as well as less resentment and hate in people with ALS. It must be pointed out that some people with ALS may value hating and resenting ALS as the best strategy for them in terms of coping and life satisfaction, and we have much to learn from them about their experiences in living with ALS.

The majority of the sample indicated a strong or moderate resentment level; a similar indication was given subjects' perception of caregiver resentment level. About a third of the sample reported sporadic episodes of hate, while less than a fifth of the subjects indicated to always hate the disease. The current study suggests a prevalence of these distressing emotional experiences that is high enough to warrant investigation of the nature of these experiences and the meanings that they have for the people having them.

We postulate that there may be cognitive interpretations of experiences of living with ALS that may increase the likelihood of experiencing resentment and hatred. If so, then clinicians could

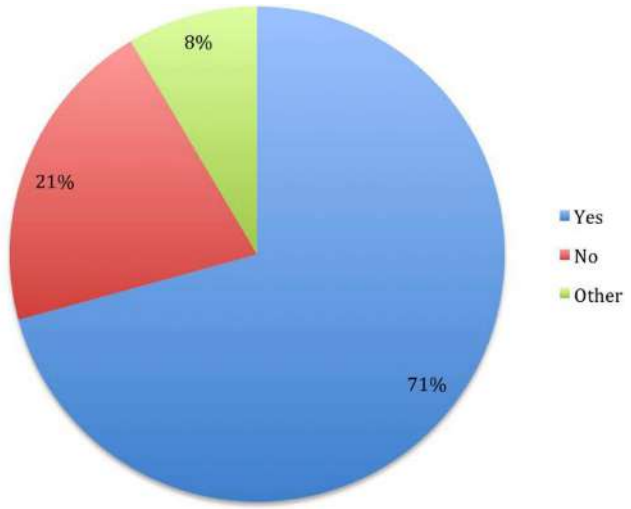

FIGURE 1 | Do you have hope that you could live 10 years or longer regardless of whether an effective pharmaceutical treatment were to be discovered? (*N* = 82).

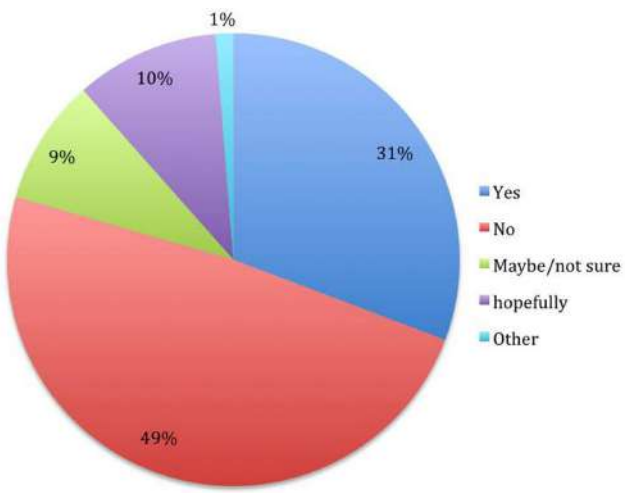

FIGURE 2 | Do you believe that there will be a cure for ALS in your lifetime? (*N* = 78).

work with ALS patients to learn to interpret events in ways that are less emotionally and physiologically distressing. This is what was personally observed by Oster, first author of this paper and an 18 year survivor of ALS, in his self-case study. Oster has experienced much more positive experiences of living with ALS through working with a psychoanalyst psychologist for over 12 years, and experiences less hate and resentment toward ALS. Oster states that he has learned to see the world differently, based to a large extent upon learning to interpret and understand living with ALS differently (unpublished data). There are no or very few studies about psychological interventions in ALS, as recently pointed noted (Pagnini et al., 2012b). However, psychological treatments with people with other chronic illnesses presented a high capacity to improve the well-being and to reduce the anger response, promoting acceptance (Telford et al., 2006).

Other researchers have evaluated that patient hopefulness is the result of an active style of coping, although their construct of hope was more comprehensive than our definition (Fanos et al., 2008). Furthermore, previous research has demonstrated that lower levels of well-being are associated with reduced longevity (Pagnini et al., 2012a); therefore, we believe that it would be worthwhile for additional research on the relationship between the variables of hate, resentment, and hope in relationship to well-being to help understand whether these variables factor into longevity with ALS.

The analyses of the relationships among resentment, hate, and hope provide interesting results. Subjects who reported hope of living 10 years or more reported less hate and resentment toward ALS. Further research is required to understand hope in relationship to hate and resentment, and to answer the following questions. Is hope in ALS protective regarding the experience of hating and resenting ALS? And/or, do tendencies to experience greater hate and resentment regarding losses, challenges, limitations, and frustrations lessen hope in people with ALS? Aside from the relationship of lower levels of hating ALS being associated with being married and having hope of surviving 10 years post-diagnosis, it is unclear from our findings what causes some people to always hate ALS and others to never hate it. Research is needed to understand the meanings and experiences of the people who always hate ALS and those who report to never hate ALS.

Levels of hate and resentment were correlated; moreover, subjects' estimation of the level of resentment in the caregiver was related to their own resentment level, without statistical differences between them. To our knowledge, this is a new finding, yet there is the issue that our research relied upon the perception that the person with ALS has of their caregiver. So, we do not know the extent to which this finding reflects actual symmetry between the person with ALS and their caregiver. Researchers have demonstrated symmetry between people with ALS and caregivers in regards to distress, but this has not been previously studied in regards to resentment (Rabkin et al., 2000).

There were differences in gender in the report of resentment and hate related to the illness. Women indicated higher level of resentment and a higher level of hate, with the latter emotion only expressing a tendency toward significance. The novelty of this data suggests caution in its interpretation, but a possible explanation is that women are more devastated by being robbed of their caregiving role as well as by being forced into being a recipient. Cultural norms may play a role in gender differences found. Cultural norms emphasize the physical appearance of the woman being linked to feeling valued, loved, included, but the perception of the body after the diagnosis of ALS may be related to discard, pity, and contempt. Furthermore, men may have a tendency to have been recipients of nurturing and caregiving from not only mothers but also wives, therefore adapting more easily to being put in the role of being taken care of. Further investigations and data are required regarding these cautious interpretations, as well as regarding whether or not some of women's greater resentment than men about ALS is related to some extent to greater distress with receiving the

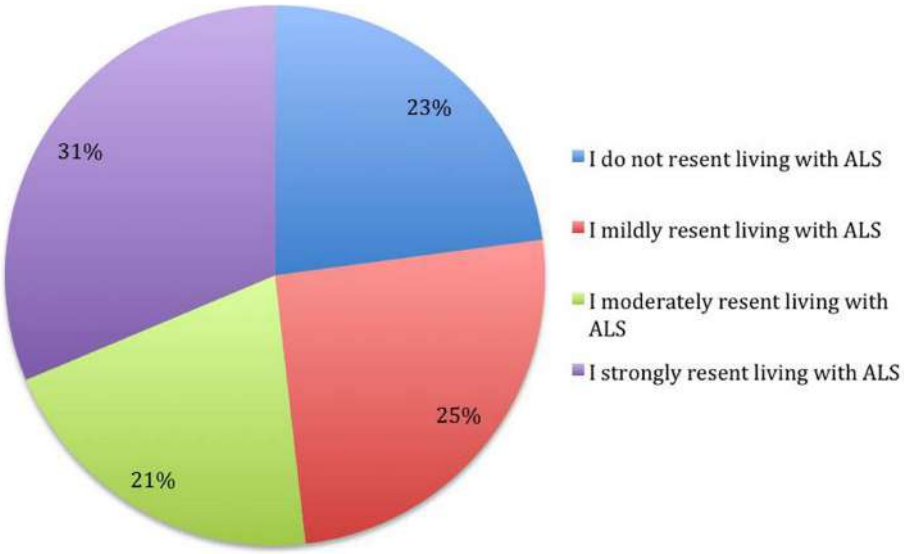

FIGURE 3 | What statement best describes the level of resentment that you feel about living with ALS? (*N* = 83).

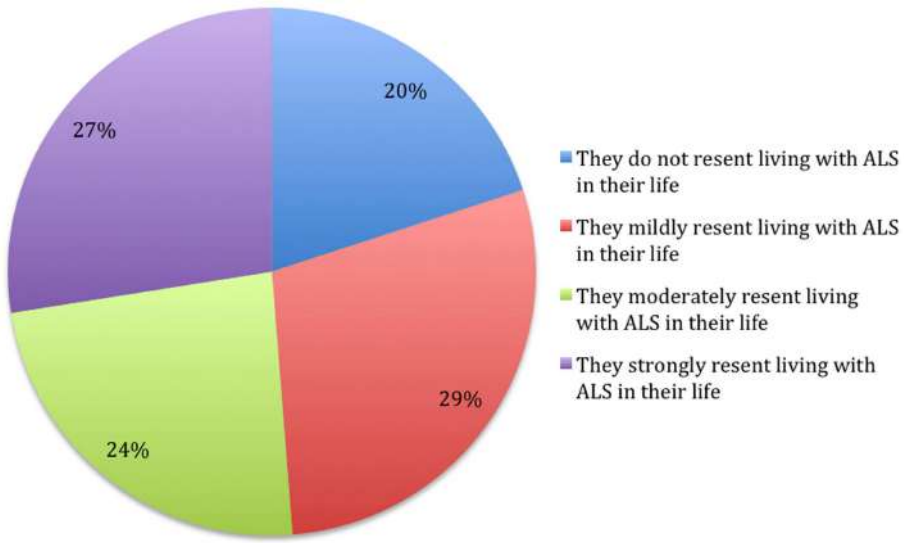

FIGURE 4 | What statement do you guess best describes the level of resentment that your primary caregiver feels about living with ALS in their life? (*N* = 80).

very personal assistance required with urination and bathing as a recipient of caregiving.

The time since diagnosis is another issue that discriminates hate and resentment levels, as well as reported hope. In our sample, subjects who have had ALS for a longer time reported higher levels of hope as well as lower levels of both hate and resentment. A possible explanation to these findings may be related to the relationship established with the illness and a grief elaboration process. Living with the illness could promote its acceptance; therefore, the amount of time spent with ALS may play a positive role in diminishing hate and resentment toward the illness. Moreover, the reason why people who survive ALS longer have more hope of living longer could be related to the course of the illness being less quick than initially perceived, resulting in less hate and resentment toward ALS.

In the light of our findings, and because of the quality of life issues involved, we suggest that clinicians attempt to understand the meanings of patients' hate and resentment toward ALS and not take it at face value. Although, it appears that the passage of time may in many cases increase hope and decrease both hate and

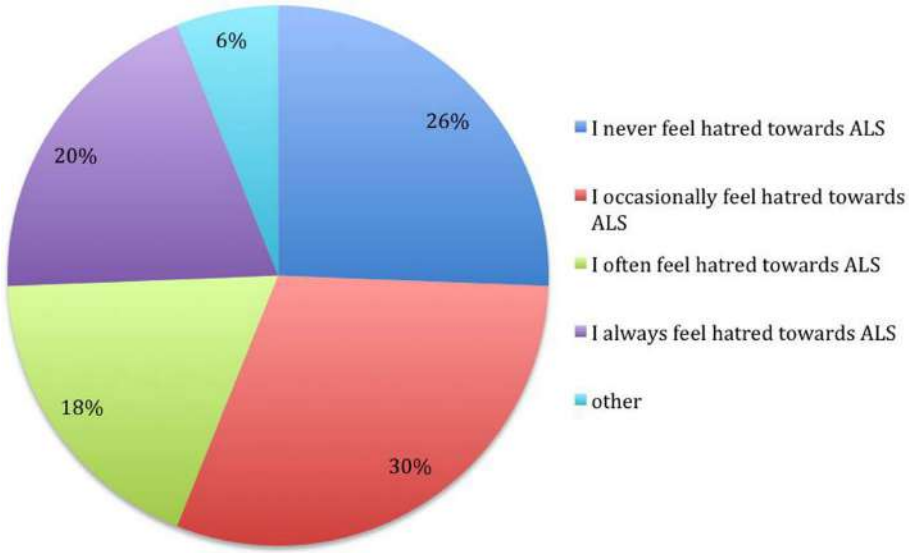

FIGURE 5 | What statement most accurately describes your feelings in the last 6 months regarding "hating" ALS? (*N* = 82).

resentment, it is possible that some people could get stuck in the grieving process because of the immensity of the losses that may occur with ALS.

The investigation of hope provided interesting results about the motivation toward following medical indications. The subjects who have the hope to live more than 10 years or more reported, as a group, more willingness to follow a strict nutrient-dense diet if scientific research indicated that such a diet increased life expectancy by 1 year, but declared that they would not agree to consume drugs with uncomfortable side effects, even if these would increase life expectancy by 1 year. It seems likely that people who already have the hope to maintain a positive level of quality of life may be more interested in maintaining it, as compared to worsening their quality of life to gain 1 year of survival.

It is noteworthy that some subjects, whether or not they have the hope of 10 years survival, would be willing to sacrifice 1 year of life rather than eating a nutrient-dense diet if it were demonstrated to be healthier for ALS. 18% (14 subjects) of the population in our study would be willing to refrain from a healthier diet, instead of extending their lives by 1 year. Slightly less than 5% (four subjects) of the population in our study would be willing to refrain from a healthier diet, instead of extending their lives by two or more years. To our knowledge, this is the first time that people with ALS have reported and been documented to be willing to sacrifice months off of their lives in order to eat whatever they desire. One subject in our study, whose response was categorized as "other" stated that they would only follow a life extending diet if it tasted good. Others reported that it would depend upon the quality of life that they would have, if they were to practice the hypothetical diet.

Additional research is required to discover what the meanings are for the people with ALS who would cut their lives short, rather than choose to focus on their longevity through life style changes. It appears that there is a cost-benefit analysis going on in terms of time, given that over three times as many subjects (14 of them) would refrain from a nutrient-dense diet that would extend their lives for a single year, as compared to the subjects (only four of them) who would refrain from consuming a nutrient-dense diet that would extend their lives by two or more years. Research is needed to understand whether or not actual self-care dietary behavioral choices are predictive of longevity in a way other than what has been established about people with ALS who maintain weight having a greater longevity (Paganoni et al., 2011). Another area deserving research is whether or not hope in ALS is related to longevity, mediated by self-care dietary behavioral choices, dietary, or otherwise.

Caregivers' resentment, as perceived by the subjects, is related to subjects' reports of whether their dietary habits have changed as a result of losses associated with the disease. Perhaps this reflects a sense of guilt in the person with ALS, in relationship to the caregiver to whom they may feel burdensome. Some previous papers have reported on a sense of feeling guilty toward the caregiver as one of the most distressing issues for a person with ALS (Bolmsjo, 2001). It seems possible that if a subject indicates higher caregiver resentment, that the reported perception of caregiver's resentment could be to some extent a projection of an inner sense of guilt. Another possibility is that the person may accurately perceive the high resentment of the caregiver, and therefore experience some guilt that leads to his/her having a lower enjoyment of life, including dietary habits. Clinically addressing and attenuating caregivers' resentment could possibly reduce the ALS diagnosed persons' resentment level, to the extent that part of the latter's resentment of ALS is related to being dependent upon a caregiver with high resentment. Previous research has demonstrated that caregiver depression is related to the depression experienced by the patient, and therefore, addressing caregiver depression may also reduce patient distress (Pagnini et al., 2010, 2012a).

This study presents some limitations. The use of non-validated instruments, such as the survey questions that we have created, may reduce the validity of the results. Further studies with validated questionnaires about anger, hate, and resentment are warranted. The cross-sectional design does not allow any causal inferences between variables, even if these can be discussed in the interpretation. Moreover, the sample size was small and it is possible that some correlations would be underestimated. Finally, the choice of an Internet-based survey may limit the external validity of the study to people with ALS who have access to Internet, and who can easily communicate with a keyboard, augmentative communication, or with personal assistance. The self-selection of the sample may further reduce the generalizability of results, and there was no premorbid attitudinal assessment to compare to the current attitudes. The only inclusion criteria was a self-reported diagnosis of ALS, and we had no chance to verify this information. However, subjects did not receive any compensation, therefore we consider the chance of subjects' participation without ALS not probable. Moreover, there is a balance between male and females in our sample, but it seems that ALS is lightly more prevalent in males, suggesting that the sample could be non-completely representative. Therefore, further studies with representative samples, longitudinal and experimental designs are required to confirm and deepen the findings presented in this paper.

CONCLUSION

The present study is a first attempt to investigate hate, resentment, and hope in ALS, in relationship to each other and in relationship to the willingness to follow a strict nutrient-dense diet, if it were shown to increase longevity. We conducted an online survey, where people with ALS were directly invited to provide answers. Results indicate that there is a massive presence of hope in our sample, with heterogeneous levels of hate and resentment; the three constructs were interrelated. Subjects with hope of living 10 years or more were more likely to report a willingness to make dietary lifestyle changes if such changes were demonstrated to increase longevity. Resentment and hate tended to be higher in people who have had ALS for less time, and in women. People who have lived with ALS for more time expressed a higher level of hope to live 10 years or more.

The main findings of this research indicate that hate, resentment, and hope could be important issues to investigate in future ALS studies. Their roles in the acceptance process of the illness, and how hate and resentment feelings as well as hopelessness may be clinically treated, are important topics to be explored by ALS researchers and clinicians. In particular, the development of specific psychological interventions, or research about existing psychological treatments applied to people with ALS, seems important to improve patients' and caregivers' quality of life (Pagnini et al., 2012b).

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The relationship between depressive symptoms, disease state, and cognition in amyotrophic lateral sclerosis

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Cognitive impairment (CI) in amyotrophic lateral sclerosis (ALS) may present a serious barrier to a patient's wellbeing and significantly decrease quality of life. Although reports of CI in ALS without frank dementia are becoming quite common, questions remain regarding the specific cognitive domains affected, as well as how other psychological and medical factors may impact cognitive functioning in these patients. Additionally, the influence of depressive symptoms on disease processes is not known. We aimed to address these questions by completing extensive neuropsychological tests with 22 patients with ALS and 17 healthy volunteers. A subgroup of these patients also completed questionnaires to measure depressive and vegetative symptoms. We tested for overall cognitive differences between groups, the influence of physical (e.g., bulbar and limb), vegetative (e.g., fatigue), and depressive symptoms on cognitive performance, and the relationship between depressive symptoms and disease severity in ALS. Overall, patients performed more poorly than healthy controls (HCs), most notably on tests of executive functioning and learning and memory. Results suggest that true cognitive performance differences exist between patients with ALS and HCs, as these differences were not changed by the presence of vegetative or depressive symptoms. There was no effect of limb or bulbar symptoms on cognitive functioning. Also, patients were not any more depressed than HCs, however increased depressive scores correlated with faster disease progression and decreased limb function. Collectively, it is suggested that translational advances in psychological intervention for those with CI and depression become emphasized in future research.

Keywords: ALS, motor neuron disease, neuropsychology, depression, ALSFRS-r, cognition, limb symptoms

INTRODUCTION

Until recently, amyotrophic lateral sclerosis (ALS) was still considered by many a pure motor neuron disease (Pongratz, 2000), and the notion of cognitive impairment (CI) in ALS was met with much resistance until just the past several years (Bak and Chandran, 2012). It is now widely accepted that ALS is a multisystem disorder involving CI in approximately 30% of those diagnosed with the disease (Rippon et al., 2006). ALS with CI is now recognized as a subcategory of ALS (Strong et al., 2009) and is denoted as ALS*ci* (Murphy et al., 2007), which entails presentation of CI without frank dementia. Importantly, some experts propose that ALS is not a categorical disease, but rather a spectrum disorder between pure ALS and Frontotemporal Lobar Degenerative diseases, such as Frontotemporal dementia (Abrahams et al., 2000; Grossman et al., 2007; Murphy et al., 2007; Woolley and Katz, 2008; Merrilees et al., 2010).

Recent advances in the field support the need for study into cognitive problems associated with ALS (see Phukan et al., 2007). One critical reason for this research is that cognitive difficulties in patients with ALS negatively impact quality of life, and appear to be even more detrimental to quality of life than physical impairment (Goldstein et al., 2002). Personal communication with patients who believe their cognitive ability has been compromised report being negatively impacted by these symptoms and wanting help, or at least support, in this area. Additionally, CI can influence decision-making (Girardi et al., 2011), treatment compliance (Olney et al., 2005), survival (Olney et al., 2005; Flaherty-Craig et al., 2011), and even the wellbeing of caregivers (Merrilees et al., 2010).

Most studies that have identified CI in patients with ALS have utilized a comprehensive neuropsychological battery to assess performance across multiple modalities. Of these studies, verbal fluency remains one of the most sensitive measures for CI, repeatedly showing poorer performance in those with ALS compared to healthy individuals (Abrahams et al., 1997, 2000; Kilani et al., 2004; Grossman et al., 2007). These findings hold even after correcting for possible verbal production impairment (Abrahams et al., 2004). Other studies have found decreased performance in other areas of executive function (Kilani et al., 2004), memory (Abrahams et al., 1997; Hanagasi et al., 2002), and language (Hillis

et al., 2004; Raaphorst et al., 2010). Although reports of CI in ALS are becoming more common, characteristics of ALS*ci* are not well defined due to a number of factors. These include the lack of availability of valid cognitive measures that can be administered to ALS patients with significant motor or speech limitations, as well as minimal research focusing on additional variables that could also impact cognition, such as physical symptoms and mood state.

As previously mentioned, ALS*ci* is not well understood, and the involvement of physical symptoms on CI in ALS is not known. Specifically, previous research has indicated that those with bulbar onset are more likely to have ALS*ci* (Gordon et al., 2011), yet others have not supported this notion (Rusina et al., 2010). Additionally, vegetative physical symptoms of ALS may impact the interpretation of those identified with ALS*ci*. For example, it is known that fatigue, one of the most common vegetative symptoms in ALS, interferes with cognitive test performance in other patient groups (Diamond et al., 2008). For the purpose of this paper, vegetative symptoms collectively refer to changes in concentration, fatigue, appetite, sleeping, and energy level. Although these symptoms can also be specific to depression, ALS patients with physical weakness are likely to have more vegetative symptoms in the performance of daily activities rather than from depression, especially if the patient does not report other symptoms of depression such as hopelessness and guilt. Therefore, it is necessary to differentiate between physical and depressive symptoms in predicting CI in order to obtain a more accurate description of CI in patients with ALS. This may also lead to more streamlined classification of those with true CI who may need or want intervention.

Like CI, research suggests that depressive symptoms in ALS may also have a negative impact on many aspects of quality of life (Tramonti et al., 2012), and could potentially affect cognition. To our knowledge however, no studies have examined the influence of depressive symptoms on cognitive performance in ALS. Like vegetative symptoms, mood status could present a potential confound in the diagnosis of ALS*ci*. Also, depressive symptoms may increase the risk of having CI, or differentially affect cognition in patients with ALS compared to a healthy control population. These situations are likely, as depression can negatively influence cognitive performance in other diseases (Diamond et al., 2008; Sassoon et al., 2012).

The relationship between depression and prognosis or physical symptom presentation in ALS is another area of research that has received little attention, possibly due to the general report of a global positive psychosocial adjustment in these patients (Brown and Mueller, 1970; Lulé et al., 2012). Despite this view, prevalence rates of depression (McLeod and Clarke, 2007) and reports on the effect of depression on ALS are not consistent. For example, Atassi et al. (2011) reported no relationship between disease progression and depression, yet a previous study identified a significant negative impact of psychological distress on mortality outcome (McDonald et al., 1994). Using the ALS Functional Rating Scale (ALSFRS), a group in South Korea found that decreased physical functioning correlated with depressive symptoms (Oh et al., 2012), highlighting the importance of examining this relationship. Patients in this study however were on average both highly physically disabled (ALSFRS mean score of 19) and many were clinically depressed (Beck Depression Inventory mean score of 24.5). If consistent evidence supports the association of depressive symptoms with disease processes (especially while patients are still early in the disease course and without clinical depression), this would bring about new emphasis into the study of depression in ALS, ultimately leading to improved identification of those at highest risk and thus early intervention.

The overall goal of this study was to recognize if cognitive status is affected in patients with ALS early in their disease course and without severe clinical depression. We also examined other variables that may be associated with cognitive performance that could either facilitate in future early screening or confound the diagnosis of ALS*ci*. Specifically, we investigated the relationship of physical impairment, vegetative symptoms, and depressive symptoms on cognitive functioning. In addition, we tested whether depressive symptoms are associated with disease progression or physical impairment. We utilized standard neuropsychological tests to measure these relationships. Based on previous literature, we hypothesized that patients with ALS would perform at a lower level on tests within the neuropsychological battery, especially those targeting executive functioning skills. We predicted that physical, vegetative, and depressive symptoms would negatively influence cognitive performance, but that these would not be confounding variables in performance differences between patients with ALS and healthy volunteers (suggesting true cognitive impairment in the ALS group). We also hypothesized that ALS patients would have more depressive symptoms than healthy controls, and that increased depressive symptoms would be related to disease severity.

MATERIALS AND METHODS

PARTICIPANTS

Twenty-two patients with ALS participated in this study. All patients were recruited through the ALS Clinic at the University of Michigan. Patients were diagnosed by a neuromuscular physician at the University of Michigan using the El Escorial criteria for ALS. Enrolled patients were engaged in a larger longitudinal neuroimaging component of this study; therefore all patients were without any contraindications to magnetic resonance imaging (MRI), were able to lay flat on their back without respiratory distress, were not dependent on artificial ventilation, and were ambulatory. Twenty-three healthy controls (HCs) were recruited through the general community from an internet-based recruitment tool (UMClinicalTrials.org) and from flyers posted around the Ann Arbor, MI area. Participants were excluded from either group if they had a history of alcohol or drug abuse, neurological disease (other than ALS), were ever diagnosed with a psychological disorder, or were severely clinically depressed at the time of their participation. No patient was excluded from the study, and one healthy volunteer was excluded for major depression. Because we aimed to compare cognitive status in patients with ALS to a truly healthy control group, HCs at risk for mild CI (see Statistical Analysis) were also excluded from the final analysis. Participant demographic information for these final groups is displayed in **Table 1**. Signed consent from each participant was obtained, and all aspects of this study were approved by the Institutional Review Board at the University of Michigan.

Table 1 | Means and SD for demographic information by group.

Demographic variables	ALS patients	Healthy controls
Age	59 (6.6)	58 (5.0)
DH	18R*, 4L	15R, 2L
Sex	13M, 9F	5M, 12F
Education years	13.4 (2.0)	16 (2.6)
Symptom onset	17L, 5B	NA
ALSFRS-r total	37.2 (6.9)	NA
ALSFRS-r limb	16.5 (5.3)	NA
ALSFRS-r bulbar	10.0 (2.4)	NA
ALSFRS-r resp.	10.73 (1.9)	NA
MSO	26.2 (35.6)	NA

*DH, dominant hand; Education Years, number of complete years of education, considering degrees obtained; ALSFRS-r Limb, subscore from ALSFRS-r questionnaire assessing limb function (questions 4–9); ALSFRS-r Bulbar, subscore from ALSFRS-r questionnaire assessing bulbar function (questions 1 – 3); ALSFRS-r Resp., subscore from ALSFRS-r questionnaire assessing respiratory function (questions 10 – 12); MSO, months since symptom onset. *Two patients reported current dominant hand as a result of disease processes and not by preference.*

NEUROPSYCHOLOGICAL ASSESSMENTS

All participants completed a 60-min neuropsychological battery designed by a team of neuropsychologists experienced in motor diseases (lead by CP). These tests were selected to assess a broad range of cognitive skills, particularly those commonly associated with frontotemporal dementia, given the reported prevalence of such deficits in patients with ALS. Depressive and vegetative symptoms were also measured using the Geriatric Depression Scale, short version (GDS), and the Beck Depression Inventory (BDI), respectively. Not all participants completed both questionnaires. Nineteen ALS patients and 15 HCs completed the GDS, and 14 patients and 15 HCs completed the BDI. All tests and questionnaires are described below. Reliability coefficients and, when available, construct validity coefficients are given for each measurement (Strauss et al., 2006).

Mini-Mental State Examination (Folstein et al., 1975)

The Mini-Mental State Examination (MMSE) is a brief test of global cognitive function and is often used as a screen for dementia. The scale assesses a subject's orientation to time and place, instantaneous recall, short-term memory, and ability to perform serial subtractions or reverse spelling. The MMSE also measures constructional capacities (the ability to copy a design) and the use of language. Internal consistency of this test ranges between 0.31–0.96, test re-test reliability ranges between 0.80–0.95, and construct validity is modest to high in correlating with other similar tests.

Hopkins Verbal Learning Test (Shapiro et al., 1999)

The Hopkins Verbal Learning Test (HVLT) is a learning and memory test that measures initial recall (test re-test reliability 0.74), delayed recall (20 min, test re-test reliability 0.66), and discrimination recall (test re-test reliability 0.40) for a list of words read by the administrator. The test is available in multiple alternate forms with a moderate to high construct validity with other similar tests.

Faces Subtest: Wechsler Memory Scale (WMS-III; subtests – Faces) (Wechsler, 1997)

Faces is a test of visual learning and recognition memory for pictures of faces. There is an initial recall test (Faces I) and a delayed recall test (Faces II, 30 min after first exposure to the set of faces). Internal reliability for these tests is between 0.60–0.96, internal consistency is between 0.70–0.79, and construct validity is modest.

Boston Diagnostic Aphasia Examination: Complex Ideational Material (Goodglass and Kaplan, 1983)

The Complex Ideational Material (CIM) subtest of the Boston Diagnostic Aphasia Examination (BDAE) measures auditory comprehension. This task requires patients to understand and express agreement or disagreement concerning factual material that are derived from inference. Complex Ideational Material has an internal consistency of 0.80 and a construct validity score between 0.86 and 0.93. This test was originally designed for patients with aphasia, so test-re-test reliability measurements were not provided as test performance is expected to change with this group.

The Boston Naming Test (Kaplan et al., 1978)

The Boston Naming Test (BNT) is a confrontation-naming test that is largely used to measure language processing. The test consists of 60 large pen and ink drawings of items ranging in familiarity. Participants are asked to freely name each item. If the identity of an item is not known, first a stimulus cue is provided, then a phonemic cue if needed. Scores used in this study only include freely identified and stimulus-cued correct responses. Internal consistency coefficients range between 0.78–0.96 and test re-test reliability is high (0.91). Construct validity is also high.

Judgment of Line Orientation (Benton, 1983)

The Judgment of Line Orientation (JOLO) measures visuospatial ability, specifically the ability to estimate angular relationships between line segments by visually matching angled line pairs to numbered radii that form a semicircle. The internal consistency for this test is between 0.84 and 0.91 and the test re-test coefficient is 0.90. Construct validity is high when compared with other visual spatial subtests.

Digit Span (Wechsler Adult Intelligence Scale: WAIS subtest) (Wechsler, 1997)

Digit Span is a subtest from the WAIS measuring auditory working memory. This test consists of two sections measuring immediate recall of a forward and backward digit series. In this study the total cumulative score of number of correct trials was used to measure overall working memory recall. Backward digit span is more challenging and was also used as a measurement in this study. The maximum span of backward digits recalled was used; therefore this measurement was not collinear with the total cumulative score. The generalizeability coefficient for this test is high (0.80–0.89) and the test re-test coefficient for the backward subscore is marginal (0.60–0.69).

Oral Trail-Making Test (Lezak, 1995)

The Oral Trail-Making Tests (OTMT) are tests of processing speed (Trails A) and conceptual ability (Trails B). For Trails A, the subject

is required to recite consecutive numbers, from 1–25, as quickly as possible. On Trails B, subjects are asked to alternate between numbers and letters, from 1-A to 13-M. Two scores for each part are obtained – the total time and number of errors. To more accurately measure set-shifting abilities from Oral Trail-Making Test B and partial out motor speed due to possible verbal speed production impairment in patients with ALS (Abrahams et al., 2000), time (in seconds) to complete Oral Trail-Making Test B was divided by time (in seconds) to complete Oral Trail-Making Test A, resulting in an Oral Trails B/Oral Trails A ratio. This ratio results in a more statistically accurate measure to account for processing speed differences between groups. The test re-test reliability is adequate for test A and high for test B. Tests A and B correlate well with each other (0.31).

Controlled Oral Word Association Test (Benton, 1983)

The Controlled Oral Word Association Test (COWAT) is a test of verbal letter fluency using the letters C, F, and L. Participants are asked to name as many words beginning with each letter in 1 min (each). This is largely a test of executive function. The internal consistency for this test, specifically using the letters CFL, is high (0.83). Test re-test reliability is high (0.70) and construct validity is high.

Animal Naming (Sager et al., 2006)

The Animal Naming test is a categorical verbal fluency test and is used as a test of executive function. Participants are asked to name as many animals as they can in 1 min. Test re-test reliability is 0.56 and construct validity is moderately high.

Geriatric Depression Scale-Short Form (Yesavage and Sheikh, 1986)

This 15-(yes/no) questionnaire was developed specifically to measure depression in older adults. Symptoms common to normal aging and those pertaining to feelings of guilt, sexual activity, suicide, and somatic symptoms are not included in this questionnaire. Rather, this questionnaire focuses on the individual's locus of control, "... making this more suitable for subjects in hospital or long-term care" (Strauss et al., 2006, p. 1104). Therefore the Geriatric depression scale-short form (GDS) was deemed as a more valid measure of core depressive symptoms in the ALS group and was used as a measure of depression severity. The short version has a high correlation with the full version, which is moderately to highly correlated with other tests of depression (0.73–0.91). The internal consistency for the full version ranges between 0.71 and 0.84 and test re-test reliability is 0.84.

Beck Depression Inventory (Beck et al., 1996)

This 21-item likert-scale questionnaire is a brief self-report of depression. The BDI contains a number of somatic and vegetative symptoms that can overlap with physical illness, more common in older adults and especially those with motor neuron diseases. Therefore impetus for completing the BDI was to provide a measure of vegetative symptoms to asses show they may contribute to cognitive functioning. Five questions were selected to describe vegetative symptoms: 15. Loss of Energy; 16. Changes in Sleeping Pattern; 18. Changes in Appetite; 19. Concentration Difficulty; 20. Tiredness or Fatigue. The internal consistency coefficient for this questionnaire is high (0.88) and the test re-test reliability is adequate to high (0.74–0.93). The construct validity is also high.

STATISTICAL ANALYSIS

Neuropsychological test results used to compare cognitive performance between groups are listed in **Table 2**. All data is presented in raw scores. All data were examined to check for parametric analysis statistical assumptions. Results from two tests did not meet these assumptions: the Complex Ideational Material (CIM) and Oral Trails-Making Test B/A ratio scores. In the CIM, the majority of participants performed at ceiling level (maximum score of 12 points), with just one person scoring nine points. The CIM was therefore excluded from further statistical models. The Oral Trails B/A ratio score was slightly positively skewed in both groups. Therefore individual scores from the Oral Trails B/A ratio were transformed (using the natural logarithm function), which resulted in a normal distribution for both groups. IBM's statistical software package SPSS, version 19, was used to conduct all analyses.

To assure our control group consisted of truly healthy volunteers, z-scores from neuropsychological tests were examined for mild cognitive impairment (MCI). Using standard criteria established in the literature, controls were excluded for suspected MCI if they scored at or below the fifth percentile on one or more cognitive test (Royall et al., 2004; Aarsland et al., 2010). Five controls were excluded for MCI, resulting in 17 participants in the HC group.

Age and years of education were compared between groups using independent sample t-tests, which showed no age differences ($p = 0.65$) but significantly more years of education in the HC group [$t(37) = -3.65$, $p < 0.01$]. Therefore education was included as a covariate in the following statistical models.

RESULTS

All patients with ALS completed the ALS Functional Rating Scale, revised version (ALSFRS-r). The ALSFRS-r is a 12-question survey measuring physical functioning of patients with ALS and is a strong predictor of progression and survival (Kollewe et al., 2008). Limb, bulbar, and respiratory functioning are measured in this scale and the maximum total score is 48 (lower scores indicate decreased physical function). Mean ALSFRS-r score for this patient group was 37.2 ($SD = 6.9$). Additionally, all participants completed the Oldenfield handedness questionnaire and a head trauma questionnaire (Armon and Nelson, 2012). Demographic information is presented in **Table 1**.

COGNITIVE IMPAIRMENT IN THE ALS PATIENT GROUP

Using the consensus criteria developed by Strong et al. (2009), individual normalized scores were examined for each patient to identify those with possible ALS*ci*. Scores below the fifth percentile, or falling below a z-score of -1.6, were flagged. Individuals whose scores fell below this cut-off on two or more distinct tests were identified as patients with ALS*ci*.

Examining z-scores from each of the tests within the neuropsychological battery, eight of the 22 patients (36.4%) with ALS were identified as having CI. This finding is consistent with previous research showing an estimated 30% of patients with comorbid CI

Table 2 | Neuropsychological test results between patients with ALS and healthy controls.

Cognitive domain	Neuropsychological test measurement	ALS patients ($n = 22$)		Healthy controls ($n = 17$)		Group differences	
		Mean raw score (SD)	% Impaired	Mean raw score (SD)	% Impaired	*F*-value	*p*-value
Mental status/dementia screen	MMSE total score	27.41 (2.04)	na	27.65 (1.50)	na	0.31	0.58
Executive function	COWAT (CFL) total score	32.77 (9.25)	4.50	49.53 (12.62)	0.0	11.12	<0.01
	Animal Naming total score	15.91 (4.22)	36.36	22.06 (4.59)	5.8	10.04	<0.01
	OTMT B seconds	44.68 (29.62)	4.50	25.56 (15.49)	0.0	na	na
	OTMT transformed ratio (B seconds/A seconds)	1.32 (0.55)	na	1.18 (0.39)	na	1.19	0.28
Memory/learning	HVLT initial recall, trials 1–3	23.86 (5.82)	31.80	27.24 (4.13)	5.8	1.10	0.30
	HVLT delayed recall, trial 4	8.59 (2.40)	27.3	9.94 (1.39)	0.0	1.65	0.21
	HVLT discrimination score	10.18 (1.62)	18.2	11.24 (0.97)	0.0	2.68	0.11
	Faces I total score	34.86 (4.81)	4.5	39.00 (4.47)	0.0	10.390	<0.01
	Faces II total score	37.05 (4.87)	9.0	40.65 (2.78)	0.0	6.81	0.01
Attention/concentration	Digit Span total score	15.68 (3.72)	4.5	18.12 (3.33)	0.0	2.53	0.12
	Digit Span backward span	4.50 (1.06)	0.0	5.24 (1.35)	0.0	0.83	0.37
Visuoperceptual	JOLO total score	23.91 (5.38)	13.63	25.88 (4.26)	5.8	0.05	0.83
Language	BNT total score including semantic cues	56.55 (2.46)	0.0	55.94 (3.15)	0.0	3.95	0.06
Depression	GDS (ALS $n = 19$, HC $n = 15$)	2.32 (1.97)	na	1.07 (1.16)	na	(*t*) 2.17	0.04
	BDI (ALS $n = 14$, HC $n = 15$)	5.57 (3.80)	na	3.00 (2.17)	na	(*t*) 2.26	0.03
Vegetative symptoms	BDI_veg (ALS $n = 14$, HC $n = 15$)	2.64 (1.74)	na	1.67 (1.29)	na	(*t*) 1.73	0.10

MMSE, Mini-Mental State Exam; COWAT, Controlled Oral Word Association Test; OTMT, Oral Trail-Making Test; HVLT, Hopkins Verbal Learning Test; Faces I & II from the Wechsler Memory Scale III; JOLO, Judgment of Line Orientation; BNT, Boston Naming Test; GDS, Geriatric Depression Scale; BDI, Beck Depression Inventory; BDI_veg, five questions measuring vegetative symptoms taken from the BDI; % impaired, percent of participants in each group with a z-score < −1.6. Only tests used in the identification of MCI or ALSci were included. Between group statistics from the primary MANCOVA were Bonferroni corrected for multiple comparisons ($p < 0.05$), education was entered as a covariate and degrees of freedom were 1, 36. Independent sample t-tests were conducted for the GDS, BDI, and BDI_veg. GDS degrees of freedom, 32; BDI degrees of freedom, 27.

(Massman et al., 1996; Lomen-Hoerth et al., 2003; Rippon et al., 2006; Gordon et al., 2010; Raaphorst et al., 2010; Grace et al., 2011). Five of these patients scored at or below the threshold on the Animal Naming test and seven scored at or below the threshold on the HVLT. Scores from the Animal Naming and the HVLT tests were also among the most impaired scores overall in the ALS group, including scores from patients who did not meet criteria for ALS*ci*. **Table 2** indicates the percent of patients who performed below the fifth percentile on each measurement.

A MANCOVA was conducted to test the effect of diagnosis group on cognitive performance, which showed a significant difference between ALS patients and HCs, $F(13, 24) = 4.10$, $p = 0.001$, $\eta^2 = 0.69$. There was a specific significant difference between groups on Faces I, Faces II, COWAT, and Animal Naming. These statistics are shown in **Table 2**. The overall effect of education was not significant, $F(13, 24) = 1.60$, $p = 0.15$, $\eta^2 = 0.46$, however education had an exclusive effect on the BNT, $F(1, 36) = 7.04$, $p = 0.012$.

Because verbal fluency performance can be confounded by speech production impairment in patients with ALS (Abrahams et al., 2004), we examined speed (in seconds) from Oral Trails-Making Test A between groups. An independent sample *t*-test showed that verbal speed differences approached significance, $t(37) = 1.86$, $p = 0.07$. Therefore a second MANCOVA was performed to evaluate the effect of diagnosis (ALS and HC) and verbal production speed (Oral Trails A seconds) on verbal fluency (COWAT and Animal Naming) performance. There was no main effect of verbal speed, $F(2, 34) = 1.56$, $p = 0.22$, $\eta^2 = 0.08$ and no between-subjects effects of verbal speed on the Animal Naming test, $F(1, 35) = 3.07$, $p = 0.09$, or COWAT, $F(1, 33) = 1.53$, $p = 0.22$. There was still a main effect of diagnosis, $F(2, 34) = 5.63$, $p < 0.01$. These results suggest that differences in verbal fluency between groups were not confounded by verbal production speed.

PHYSICAL SYMPTOMS OF ALS DID NOT HAVE AN EFFECT ON COGNITIVE PERFORMANCE

Physical dysfunction did not predict global cognitive summary scores

The severity of physical dysfunction in patients with ALS may influence cognitive test performance. Some studies found that physical symptoms affect cognition differentially, specifically that those with more severe bulbar symptoms are more likely to have

CI (Gordon et al., 2011). To test this and the influence of physical functioning on cognition, bulbar (questions 1–3) and limb (questions 4–9) functioning were derived from ALSFRS-r subscores. These were entered into a linear regression analysis with overall cognitive performance as the outcome variable. A cognitive performance summary score was calculated for each individual by taking the summation of z-scores from each of the cognitive test measure ($M = -0.32$, SD $= 6.03$). This model was not significant, $F(2, 19) = 1.50$, $p = 0.25$, $R^2 = 0.05$. Bivariate correlations (Pearson's r) between physical symptoms and overall cognitive performance were also not significant: bulbar $p = 0.45$, limb $p = 0.12$.

Vegetative symptoms did not influence cognitive test scores

Another possible confound in a patient's cognitive status could be attributed to vegetative symptoms common in patients with ALS. We therefore created a subscore of vegetative symptoms measured within the BDI, and examined the effect of these symptoms on cognitive test performance between patients and controls. Five questions from the BDI were used, described previously. A MANCOVA was conducted to test the hypothesis that vegetative symptoms may extraneously influence cognitive test performance. Diagnosis, education, and vegetative symptom subscores were entered as independent variables. Because patients are more likely to be affected by these symptoms due to physical weakness, we predicted that patients with ALS would be more negatively affected compared to HCs; therefore an interaction term between diagnosis group and vegetative symptoms was also included in this model.

This analysis showed no main effect for vegetative symptoms on cognitive performance, $F(13, 12) = 1.31$, $p = 0.33$, $\eta^2 = 0.59$. However, vegetative symptoms did influence test performance on the Digit Span backward scores between groups, $F(1, 24) = 5.25$, $p = 0.03$, $\eta^2 = 0.18$. Even after accounting for the possible effect of vegetative symptoms on cognitive performance, there was still a main effect of diagnosis group, $F(13, 12) = 3.19$, $p = 0.03$, $\eta^2 = 0.78$. As in the original analysis, there was no effect of education, $F(13, 12) = 1.06$, $p = 0.46$, $\eta^2 = 0.54$. Also, there was no interaction effect between vegetative symptoms and diagnosis group, $F(13, 12) = 0.59$, $p = 0.82$, $\eta^2 = 0.39$.

Because only 14 patients completed the BDI, t-tests were conducted to test for demographic variable differences between patients with and without BDI data, and a MANOVA was conducted to test for a main effect on cognitive test performance. Age, education, disease duration, and progression rate (PR) did not differ between groups. There were also no differences between cognitive test scores. ALSFRS-r scores however approached significance, $t(20) = 2.04$, $p = 0.06$. The group who completed the BDI had a mean ALSFRS-r score of 39 (SD $= 4.46$) whereas those without had a mean ALSFRS-r score of 34 (SD $= 8.98$). Given the small sample size, it is possible that there was not an effect for vegetative symptoms on cognition because patients in this analysis were physically higher functioning. However, this importantly shows that patients with less disease severity still have overall poorer cognitive performance than HCs, independent of the effects of vegetative symptoms.

DEPRESSIVE SYMPTOMS IN ALS IN RELATION TO DISEASE SEVERITY AND COGNITION

Patients with ALS were not more clinically depressed than HCs

We tested the hypothesis that patients with ALS were more depressed than the HC group by conducting independent sample t-tests using scores from the GDS. ALS patient mean scores were higher on the GDS than the HC group (see **Table 2**). Although these differences were statistically significant, the mean scores did not fall within clinical range for depression. When examining individual depression scores, two participants in each group met clinical criteria for possible mild depression as measured by the GDS. Vegetative symptoms, measured from the BDI, reported by patients were not different than the HC group.

Depressive scores correlated with progression rate (PR) and limb dysfunction

The fourth major goal of this study was to determine if depressive symptoms are related to disease severity in ALS. A correlation analysis using Pearson's r-coefficient was conducted comparing GDS scores with PR. PR was calculated using the equation:

$$(\text{PR}) = \frac{(48 - \text{ALSFRS-}r \text{ Patients Score})}{\text{Months Since Symptoms Onset}} \text{ (Kollewe et al., 2008)}$$

This correlation was significant, $r = 0.52$, $p = 0.02$ (see **Figure 1**). To further examine this relationship, the ALSFRS-r was divided into three subscores measuring bulbar (questions 1–3), limb (questions 4–9), and respiratory (questions 10–12) impairment. Of these models, depression scores negatively correlated with limb dysfunction, $r = -0.72$, $p < 0.001$ (**Figure 2**). Depression scores did not correlate with bulbar ($p = 0.60$) or respiratory symptoms ($p = 0.49$), however it should be noted that the range of bulbar and respiratory symptoms in our group was small.

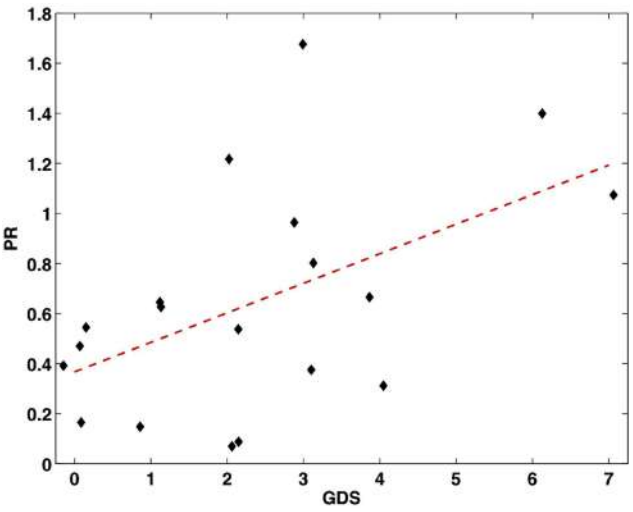

FIGURE 1 | Scatter plot showing the significant correlation between increased depressive scores from the GDS and faster progression rate (calculated by the PR equation, $n = 19$).

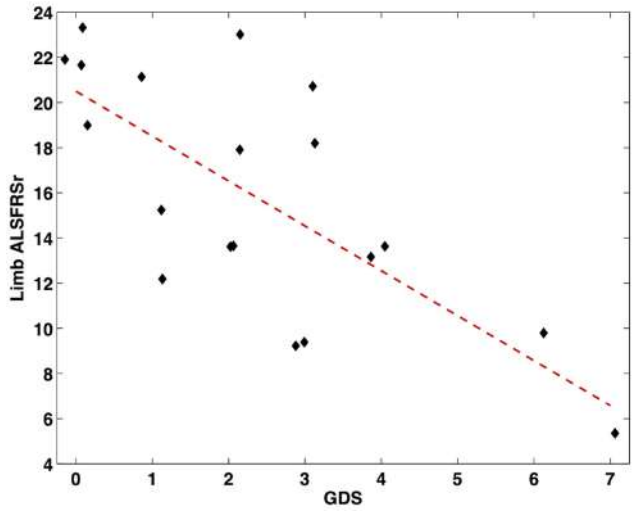

FIGURE 2 | Scatter plot showing the significant correlation between increased depressive scores from the GDS and decreased limb function measured from the ALSFRS-r ($n = 19$).

Depressive symptoms affect cognitive test performance

The final MANCOVA in this study was performed to test the hypothesis that depressive symptoms have an influence on cognitive test performance differentially in patients with ALS. Depression may negatively impact cognition, and we aimed to answer whether ALS patients are more at risk for CI if they have comorbid depressive symptoms. Therefore, an interaction variable between GDS scores and diagnosis group and main effect variables of diagnosis group, GDS scores, and education were entered into the MANCOVA to test for effects on cognitive test measurements from the neuropsychological battery.

In this MANCOVA, there was a significant interaction effect between GDS scores and diagnosis group, $F(13,\ 17) = 2.90$, $p = 0.02, \eta^2 = 0.69$. As expected, there were significant main effects of depressive symptoms, $F(13, 17) = 3.34$, $p = 0.01$, $\eta^2 = 0.72$ and diagnosis group, $F(13,\ 17) = 4.51$, $p < 0.01$, $\eta^2 = 0.78$. Examining the univariate effects on each cognitive test separately, there was interestingly not a significant main effect of depression on any single cognitive test, although the HVLT delayed recall scores approached significance, $p = 0.07$. There also was not a significant univariate effect of the interaction variable on any single cognitive test. Slopes of univariate analyses were examined to assess which group was more affected by depression on each cognitive test individually. Patients were more negatively affected by depressive symptoms on six of the cognitive test measurements (HVLT delayed recall, Faces II delayed recall, Oral Trails ratio, Animal Naming test, JOLO, and BNT), whereas the HCs were more negatively affected on five of the cognitive test measurements (MMSE, HVLT immediate recall and discrimination, Faces I immediate recall, and COWAT). This indicates there was not a specific pattern of which group was overall more affected by depressive symptoms, rather that the groups were indeed affected differently on individual cognitive domains. For example, patients appear more affected by depressive symptoms on tests of delayed recall whereas HCs appear more affected on tests of immediate recall.

DISCUSSION

There has been a recent push toward psychological intervention for patients with ALS in order to improve overall quality of life (Pagnini et al., 2012). Interventions would be better streamlined if risk factors for psychological distress were identified early, including risks for cognitive dysfunction and depression. In this study, we analyzed cognitive test performance between patients with ALS and a healthy control population. Importantly, we assessed the influence of physical and depressive symptoms on cognitive functioning in ALS, which may lead to better screening of individuals possibly at risk of having ALS*ci*. We also examined depressive symptoms in patients with ALS, and assessed if these depressive symptoms are related to disease progression or the manifestation of physical dysfunction specific to the disease process.

COGNITIVE PERFORMANCE DIFFERENCES BETWEEN PATIENTS WITH ALS AND HEALTHY CONTROLS

Results from our study corroborate previous findings, supporting cognitive performance differences between patients with ALS and HCs (Grossman et al., 2007; Strong et al., 2009). Overall, patients performed more poorly on cognitive testing than HCs, with specific deficits in executive function (verbal fluency) and visual recognition memory. Among patients identified as having ALS*ci*, the majority had impaired scores in semantic fluency and verbal learning and memory. Poorer performance in verbal fluency was not confounded by speech production speed. These findings are consistent with the literature, as verbal fluency remains the most sensitive to ALS cognitive dysfunction, and many others have noted impairment in memory and learning (Massman et al., 1996; Strong et al., 1996, 1999; Abrahams et al., 1997, 2004; Hanagasi et al., 2002; Grossman et al., 2007; Christidi et al., 2012). Utilizing neuropsychological tests that measure these cognitive domains would be most beneficial to screen for cognitive decline in a multidisciplinary ALS clinic setting, and have already been implemented in some clinics (Flaherty-Craig et al., 2009, 2011; Woolley et al., 2010).

THE EFFECT OF PRIMARY AND SECONDARY PHYSICAL SYMPTOMS ON COGNITION IN ALS

Results did not support a unique contribution of limb or bulbar function on cognition. There has been no evidence that limb onset or symptoms are related to CI, and our results support previous research that found no specific effect of bulbar symptoms (Rippon et al., 2006; Gordon et al., 2010; Rusina et al., 2010). However, research on this is not consistent, and several studies have indicated that those with bulbar onset are more likely to be cognitively impaired (Lomen-Hoerth et al., 2003; Gordon et al., 2011). It may be possible that higher reports of CI in these patients are partly due to speech-motor impairment confounds, as a recent meta-analysis of 554 non-demented individuals with ALS did not find a relationship between CI and bulbar onset ALS (Raaphorst et al., 2010). Although we did not find an effect of bulbar symptoms on cognitive function, the number of patients with bulbar onset ALS

were disproportionally less than those with limb onset, therefore our study was limited in that we could not conduct a comparative analysis between onset subtypes. Additionally, there was a small range of scores for bulbar symptoms, as measured by questions 1–3 in the ALSFRS-r (see **Table 1**), which may have contributed to our null result. Regardless, the involvement of bulbar symptoms on cognition, if any, should be further investigated to establish consensus.

One of our primary goals was to test whether vegetative symptoms confound or mask the interpretation of CI in ALS. Our results indicate, however, that these symptoms did not contribute to cognitive performance differences between patients with ALS and HCs. Although against our hypothesis, these results suggest that secondary physical symptoms, such as fatigue, collectively do not interfere significantly with test performance in patients with ALS. This finding was from a subgroup of patients in our study with overall high physical functioning, suggesting that CI manifests very early in the disease process. This finding supports ALS*ci* as a true variant of the disease, and increases the importance of understanding CI in ALS.

RELATIONSHIP BETWEEN DEPRESSIVE SYMPTOMS, PHYSICAL SYMPTOMS, AND COGNITION IN ALS

Depression contributes to decreased quality of life in patients with ALS (Tramonti et al., 2012), however our study indicated that as a group patients with ALS were no more likely to be depressed than a HC population. Although these results are consistent with recent reports (Averill et al., 2007; Atassi et al., 2011) that claim prevalence rates of depression are low in ALS, our study was limited by a small sample size and was not representative of a valid prevalence-rate study. Importantly, we found that increased depressive symptoms were associated with both disease progression and the severity of limb dysfunction. Severe global physical dysfunction has been shown to correlate with clinical depression (Oh et al., 2012), and now this effect has been demonstrated in a physically high functioning group without clinical depression (and using the revised version of the ALSFRS). Additionally, this relationship was most sensitive to limb dysfunction, suggesting those with more severe limb impairment may be at most risk. Given these findings, in conjunction with evidence for increased mortality risk in those with psychological distress (McDonald et al., 1994), future research on depression treatment and its association with survival should be emphasized.

Another important finding from our study indicates that depressive symptoms had an effect on cognitive performance. Although novel in the ALS literature, the relationship between depression and cognition has been demonstrated among other diseases (Diamond et al., 2008), and it has even been suggested that depression treatment could lead to improved cognitive performance (Sassoon et al., 2012). Likewise, a recent meta-analysis found that cognition can predict depression status, which could be targeted to increase treatment efficacy for depression (Phillips et al., 2010). Although there are no reports of depression treatment improving cognitive functioning or vise versa in ALS, these could potentially become important avenues for future translational research.

LIMITATIONS AND CONCLUSIONS

Limitations

A major limitation in our study is that we were not able to test other factors that have been found to influence cognitive performance in patients with ALS. For example, Kim et al. (2007) found that patients with reduced forced vital capacity (FCV) performed significantly worse on tasks measuring memory retention/retrieval and verbal fluency than patients with normal vital capacity. Moreover, it has been suggested that impaired cognition might be reversible to some degree with increased vital capacity (Kim et al., 2007; Strutt et al., 2012). We suspect that patients in our study did not have impaired FVC for two reasons: they were enrolled in an MRI study and therefore able to lay flat on their back for more than 1 hour without respiratory distress, and scored near maximum on the ALSFRS-r questions measuring respiratory symptoms. Regardless, we did not explicitly acquire FVC measurements and were therefore unable to take into account this possible confound in our data.

Similarly, pseudobulbar affect is another symptom that may have a differential effect on cognition, and previous research has suggested that those with this symptom may be more at risk for CI (Abrahams et al., 1997). Again, we did not measure pseudobulbar affect symptoms and are therefore unable to account for this possible influence on cognition.

Our study also lacks a causal interpretation. We found that depressive symptoms and cognitive performance are related, but because we were unable to manipulate depressive symptoms or cognitive performance we were unable to identify the exact direction of this relationship. Additionally, our study showed that depressive symptoms are related to disease progression and limb dysfunction, yet it cannot be concluded whether increased depressive symptoms caused or directly influenced disease state. It is suggested that future studies examine depression and cognition intervention in order to identify a directional change in either disease state or cognitive performance.

Another major limitation in our study is the small sample size of groups. It is common for studies examining cognitive performance to include more than 100 participants, yet our study only compared 22 patients to 17 HCs. This is often a limitation in many rare disease population studies, however, and is especially common in the ALS literature. Future research would benefit from multicenter pooling of data, as suggested by Turner et al. (2011), in order to acquire larger sample sizes and gain higher statistical power.

In line with our small sample size, our analysis examining the effect of vegetative symptoms on cognition between groups was especially limited because only 14 patients completed the BDI. Those who completed the BDI were less severe in their disease symptoms. This analysis cannot therefore be generalized to the whole group in our study. However, this importantly shows that patients with less disease severity still have overall poorer cognitive performance than HCs, strengthening the finding that CI is a true symptom of ALS. The role of vegetative symptoms should be further explored, including larger sample sizes and patients with varying degrees of disease severity.

Conclusions

Overall, this study supported previous findings that CI is a symptom in approximately 35% of patients with ALS, and that patients overall perform worse than HCs in tests of executive dysfunction and learning and memory. Cognitive performance differences remained after accounting for variables including vegetative symptoms, physical dysfunction, and depressive symptoms. Additionally, we report that increased depressive symptoms are related to faster disease progression and greater limb dysfunction in patients with ALS. We therefore suggest that future research investigate the effects of depression therapy in patient care.

Although CI can significantly contribute to decreased quality of life for patients with ALS, research in this area is limited and often lacks a translational emphasis. Importantly, there is currently no treatment for patients who suffer from CI in ALS. Research though has highlighted several avenues to pursue in investigating CI intervention, including improving FVC (Kim et al., 2007; Strutt et al., 2012), treating pseudobulbar affect (Abrahams et al., 1997), and now therapy for depressive symptoms. Conversely, CI treatment may also improve depressive symptoms. We emphasize that future research focus on effective psychological or clinical interventions that may improve quality of life caused by CI or depression, and that these interventions be applied in future multidisciplinary ALS clinics.

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Self perceived emotional functioning of Spanish patients with amyotrophic lateral sclerosis: a longitudinal study

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Background: ALS is a neurodegenerative disease of the entire motor system that most frequently ends with respiratory arrest in few years. Its diagnosis and the rapid progression of the motor dysfunctions produce a continued emotional impact. Studies on this impact are helpful to plan adequate psychotherapeutic strategies. **Objective:** To assess and analyze: First: How the patients with ALS perceive their emotional health. Second: The emotional impact of their physical disabilities. Third: The physical disabilities with highest emotional impact. Fourth: The feelings with highest emotional impact. **Methods:** Up to 110 Spanish patients with ALS were assessed less than 1 year from diagnosis, then twice more at 6 month intervals, using the ALS Quality of Life Assessment Questionnaire (ALSAQ-40) validated for use in Spanish. Descriptive analysis and correlation between variables were obtained. **Results:** Worries about the future, of lack of freedom, and of being a burden were prevalent feelings. On average depression was felt only "sometimes." Only 25% of the variations in the emotional state were explained by changes in the physical state at first evaluation, and 16% at the last one. Emotional functioning correlated significantly with the physical disabilities at first and second evaluation, less so at third. Communication disabilities always had the highest impact. Depression at first evaluation and hopelessness at the next two evaluations had the highest emotional impact. Hopelessness did not correlate with any physical disability at the third evaluation. On the whole, emotional dysfunction was self perceived as intermediate (between none and worst), and remained stable at 1 year follow up, in both bulbar and spinal onset patients. **Conclusions:** Physical dysfunctions *per se* have a limited role in patients´ emotional distress. Communication disabilities, as well as feelings of depression at early stages of illness, and of hopelessness later on, had the most impact. This requires their careful therapeutic attention. On average, Spanish patients with ALS cope with their disease, overcoming depression, which is not felt often, and with just mid levels of emotional dysfunction.

Keywords: amyotrophic lateral sclerosis, ALS, quality of life, emotional functioning, ALSAQ-40, self evaluation, depression, hopelessness

INTRODUCTION

ALS causes a progressive and generally rapid degeneration of the entire motor neuron system and, as a result of the subsequent muscle denervation, atrophy and weakness of the skeletal muscles, including limbs, bulbar, and respiratory muscles. Mean survival is about 3.5 years. 50% of patients may survive 3 years, 20% 5 years, and less than 10% 10 years. Minor cognitive deficits have been documented in up to 50% of patients, but 5–13% of patients may also develop frontotemporal dementia (FTD). ALS and FTD may have genetic overlapping (Mora Pardina, 2011). At present, ALS does not have a cure, or even a treatment that patients might perceive as clinically significant. Patients experience the progression of their disease as their physical disabilities progress and extend relentless. People suffering from ALS go through a tremendous amount of continuous emotional distress, right after a shocking diagnosis. The rapid decline in skeletal muscle strength causes physical dependence up to for the basic activities of daily life (ADL), which entails complex and mixed emotional reactions. The disease affects not only the patient but also their caregivers and family members, all of whom face hard emotional challenges that interrelate with those of the patient (Salas and Lacasta, 1999; Pagnini et al., 2010a,b).

We often observe that severe physical deficits do not systematically correlate with increased levels of depression, self perception of poor quality of life (QoL), or high emotional distress (Salas and Lacasta, 1999), as others have also observed (Pagnini, 2012). Moreover, the impact the disease has on emotional well-being differs significantly between individuals, and the psychological reaction of the patients to their disease and their ability to cope has an effect on the disease's evolution (Chiò et al., 2004; Roach et al., 2009; Montel et al., 2012). Therefore, the traditional assumption of a tight correlation between rapidly progressive severe physical

disabilities and emotional distress ought to be reconsidered. To study the relationship between the different physical disabilities caused by the disease and the emotional impact they may produce for the patient may contribute to better understanding and treatment of the emotional distress that ALS patients and their families endure. We understand that the way patients cope with their disease may be influenced by their cultural background; this is the first study to look at a Spanish population.

OBJECTIVE

To assess and analyze, at different times during their disease:

First: How the patients with ALS perceive their own emotional health.

Second: The emotional impact of each one of their physical disabilities.

Third: The physical disabilities with the highest emotional impact.

Fourth: The feelings with the highest emotional impact.

MATERIALS AND METHODS

MEASURING TOOL

We considered the ALS Assessment Questionnaire (ALSAQ-40) to be the most appropriate measuring tool for our objectives. The ALSAQ-40 is a specific state of health self appraisal questionnaire for ALS patients that looks at physical and emotional areas considered important by patients (Jenkinson et al., 1999; Epton et al., 2009). The ALSQ-40 has been validated for use in the Spanish language (Salas et al., 2008).

The ALSAQ-40 consists of 40 questions assessing four physical and one emotional area or dimension as self perceived by the patient. These are Physical Mobility (MOB), Independence/ADL (ADL), Eating and Drinking (EAT), Communication (COM), and Emotional Functioning (EMO). The first four dimensions assess physical deficiencies or disabilities that occur along with the disease. The fifth area evaluates the way that the patient deals emotionally with the disease. Each question or item is scored 0 to 4 according to the frequency of the symptom or feeling (never, rarely, sometimes, frequently, always). From the direct scores it is possible to obtain for each dimension an index ranging from 0 (best state of health) to 100 (worst state) which allows comparisons to be made between dimensions or over time. This ALS specific QoL measuring tool has demonstrated high validity, consistency, and reliability and appears sensitive to changes that have an impact on the overall status of patients (Jenkinson et al., 1999; Epton et al., 2009). It has been validated in different languages (Yamaguchi et al., 2004; Maessen et al., 2007; Salas et al., 2008; Palmieri et al., 2010; Pavan et al., 2010).

PATIENT SAMPLE AND METHODS

A total of 231 Spanish ALS patients were originally included in a 4-year long study. All were diagnosed with probable or definite ALS according to the El Escorial diagnostic criteria. None had clinical evidence of FTD, and all were receiving treatment with riluzol, the only approved ALS drug. They were living in different regions of Spain but they attended the ALS clinic at differing intervals. Of the total, only 110 patients whose first assessment was done no later than 12 months after diagnosis have been included in this study, in order to ensure a homogenous sample in terms of disease timeline. The evaluation of patients was longitudinal. Each patient filled out the questionnaire at three different times at 6 month intervals. Responses were always written or dictated by the patient. The questionnaire was first mailed accompanied by a request and an explanatory letter, and it was returned in clinic or by mail. The second and third evaluations were done in clinic or at home if the patient could not attend the clinic, and then mailed to us. The questionnaire could be completed in 10 min.

STATISTICAL ANALYSIS

Independent or explanatory variables were age, gender, site of onset (bulbar vs. spinal), time from onset of symptoms, time from diagnosis, and 30 functional variables, questions or items taken from the physical areas of the ALSAQ-40: Items 1–10 (MOB), 11–20 (ADL), 21–23 (EAT), and 24–30 (COM). Dependent variables were the 10 items, 31–40 (EMO) from the emotional dimension. These are:

1. I have felt lonely
2. I have been bored
3. I have felt embarrassed in social situations
4. I have felt hopeless about the future
5. I have worried that I am a burden to other people
6. I have wondered why I keep going
7. I have felt angry because of the disease
8. I have felt depressed
9. I worried about how the disease will affect me in the future
10. I have felt as if I have no freedom

The statistical analyses were descriptive, of correlation (regression analysis, Pearson's correlation), and of mean differences (t-test for independent samples), using SSPS v.15.0 for Windows, Microsoft Excel, and EPI INFO 2000.

RESULTS

DEMOGRAPHY

The sample size was 110 patients, 50 women and 60 men. 70 patients had spinal onset, 40 had bulbar onset (**Table 1**). Mean age at the first evaluation of 59 ± 14 years. Mean time between diagnosis and first assessment was 5.8 ± 4.0 months. The second evaluation was completed 5.7 ± 1.5 months after the first one by 76 patients (69.1%). The third assessment was filled out 6.5 ± 1.0 months later by 52 patients (47.3%).

SELF PERCEPTION OF EMOTIONAL HEALTH

In spite of increasing scores in the physical areas (MOB, ADL, EAT, COM) as the disease progresses, the emotional area (EMO) scores did not significantly increase (t-test for independent samples;

Table 1 | Sample distribution by gender and site of onset.

	Bulbar	Spinal	Total
Women	24 (21.8%)	26 (23.7%)	50 (45.5%)
Men	16 (14.6%)	44 (39.9%)	60 (54.5%)
Total	40 (36.4%)	70 (63.6%)	110 (100%)

Table 2). During the three evaluations, there are no significant differences in EMO between patients with bulbar and spinal onset, in spite of them having significant differences in physical functions: higher MOB scores in spinal onset patients, and higher EAT and COM scores in bulbar onset patients, as expected (**Table 2**). During the study period, mean EMO scores remain at around mid level, between best and worst. There are no significant differences in EMO scores between the first and third evaluations (1.74 points), and even less between the second and third evaluations (0.33 points; **Figure 1**).

At the first evaluation, less than 12 months after diagnosis, the feelings most often felt (that is, a score higher than 2: "*sometimes*") were worries about how the disease will affect the patient in the future (2.77), and feelings of being a burden to others (2.45), of lack of freedom (2.24), and of hopelessness (2.21). Anger at the disease (2.00) and depression (1.94) came after, but scored higher in patients who had been diagnosed less than 6 months ago (**Table 3**). At the second evaluation, about 6 months later, the feelings most often felt remain the same: worries about the future (2.66), lack of freedom (2.64), being a burden (2.53), hopelessness (2.33), and anger (2.22). Depression remained lower than 2 (1.91). At the third evaluation, 1 year after the first one, feelings of lack of freedom (2.98), worries about the future (2.73), and of being a burden (2.60) got close to a score of 3: "*frequently*." Hopelessness (2.21), anger (2.06), and depression (2.02) maintained similar scores to the first evaluation (**Table 3**).

EMOTIONAL IMPACT OF PHYSICAL DISABILITIES

To calculate how much the physical disability may be directly responsible for the emotional distress experienced by the patients,

Table 2 | Mean and SD for each area in bulbar and spinal onset.

	MOB		ADL		EAT		COM		EMO	
	Bulbar	**Spinal**	**Bulbar**	**Spinal**	**Bulbar**	**Spinal**	**Bulbar**	**Spinal**	**Bulbar**	**Spinal**
Maximun score	40	40	40	40	12	12	28	28	40	40
First evaluation	14.5 ± 11.4	19.8 ± 9.7	18.1 ± 12.9	20.6 ± 11.6	8.1 ± 3.6	1.9 ± 2.9	20.6 ± 7.5	4.6 ± 6.1	19.7 ± 13.1	17.4 ± 8.4
Second evaluation	19.3 ± 13.1	25.1 ± 11.9	23.9 ± 13.3	25.4 ± 11.6	9.4 ± 3.4	2.2 ± 3.5	23.5 ± 6.5	8.8 ± 9.3	21.0 ± 9.7	19.1 ± 10.5
Third evaluation	21.6 ± 12.9	29.4 ± 10.9	24.9 ± 12.7	30.7 ± 11.3	9.6 ± 2.4	4.3 ± 4.4	23.0 ± 5.6	11.6 ± 10.2	19.3 ± 9.4	20.3 ± 11.7

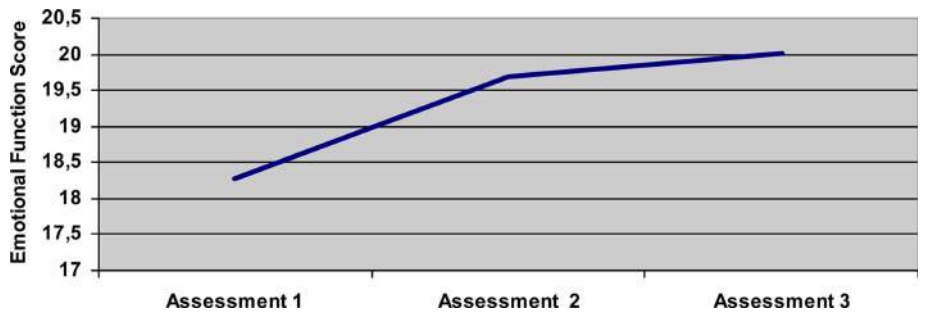

FIGURE 1 | Evolution of EMO along the three evaluations for the total sample.

Table 3 | Mean scores and SD of EMO items at the three evaluations.

EMO items*	First evaluation	Second evaluation	Third evaluation
1. I have felt lonely	0.98 ± 1.3	1.16 ± 1.5	1.10 ± 1.5
2. I have felt bored	1.30 ± 1.3	1.64 ± 1.5	1.67 ± 1.4
3. I have felt embarrassed in social situations	1.07 ± 1.3	1.10 ± 1.4	1.15 ± 1.3
4. I have felt hopelessness about the future	2.21 ± 1.2	2.33 ± 1.4	2.21 ± 1.5
5. I have worried about being a burden to other people	**2.45 ± 1.2**	**2.53 ± 1.2**	**2.60 ± 1.4**
6. I have wondered why I keep going	1.30 ± 1.4	1.49 ± 1.5	1.56 ± 1.5
7. I have felt angry because of the disease	2.00 ± 1.4	2.22 ± 1.4	2.06 ± 1.5
8. I have felt depressed	1.94 ± 1.2	1.91 ± 1.3	2.02 ± 1.4
9. I have worried about how the disease will affect me in the future	**2.77 ± 1.0**	**2.66 ± 1.3**	**2.73 ± 1.4**
10. I have felt as if I have no freedom	**2.24 ± 1.4**	**2.64 ± 1.5**	**2.98 ± 1.3**

**Items are scored as: Never = 0, Rarely = 1, Some times = 2, Frequently = 3, Always = 4.*

Bold indicates higher values that are most significant.

we carried out a dispersion diagram and calculated its linear regression. We used the EMO score as dependent variable and the sum of the scores of the physical areas (MOB, ADL, EAT, COM) as independent variables. The null hypothesis establishes that there is no relationship whatsoever between the two variables. To calculate the linear regression with 5% error and 95% confidence interval, we obtained $y = 8.298 + 0.191x$ with a correlation coefficient $R = 0.51$ and a determination coefficient of $R^2 = 0.25$. This indicates that only 25% of the variations that occur in the emotional state are explained by the changes in the physical state. The same analysis at the last evaluation produced the linear regression equation $y = 7.80 + 0.16x$, with a correlation coefficient of $R = 0.42$ and a determination coefficient of $R^2 = 16$. This shows an even smaller relationship between emotional and physical functions: only 16% of the variations that occur in the emotional state at the third evaluation, when patients experience more severe disabilities, are explained by the variations in the physical state (**Figure 2**).

PHYSICAL DISABILITIES WITH HIGHEST EMOTIONAL IMPACT

At the first evaluation there were significant correlations between EMO and COM, MOB and EAT ($p < 0.01$; bilateral, Pearson's correlation) in that order, and less significantly with ADL ($p < 0.05$; **Table 4**). At the second assessment there were significant correlations with all four physical areas ($p < 0.01$), the highest seen with COM, then with ADL (**Table 5**). At the third evaluation, the highest correlation continued being with COM ($p < 0.01$), and less so with MOB and EAT ($p < 0.05$; **Table 6**).

FEELINGS WITH HIGHEST EMOTIONAL IMPACT

Since physical dysfunctions were only partially responsible for the emotional impact, with an impact ranging from 25% at first evaluation to 16% at last evaluation, as shown in section 2, we assessed correlations between the different emotional states in EMO and the total EMO. To assess which emotions are elicited by the different physical disabilities, we calculated correlations between each EMO item and MOB, ADL, EAT, and COM (**Tables 7–9**). At the first evaluation all EMO items correlated highly with total EMO ($p < 0.01$ bilateral). The highest were items 8 on depression (Pearson $r = 0.81$), 7 on anger ($r = 0.75$), and 6 on keep going ($r = 0.74$). Item 8 on depression correlated highly ($p < 0.01$) with disabilities in MOB ($r = 0.27$) and COM ($r = 2.5$), and less so ($p < 0.05$) with ADL and EAT. All of them significantly less than with EMO ($r = 0.81$). Item 7 on anger correlated highly with MOB, COM, and ADL ($p < 0.01$) and less so with EAT ($p < 0.05$). Item 6 on keep going correlated highly with EAT, COM, and MOB. In all cases, the correlations were at much lower levels than with EMO (**Table 7**).

At the second assessment all EMO items kept a high correlation ($p < 0.01$) with total EMO. The feelings with highest correlations were items 4 on hopelessness ($r = 0.85$), 8 on depression ($r = 0.84$), and 10 on lack of freedom ($r = 0.78$). Item 4 on hopelessness and 8 on depression correlated highly with COM ($r = 0.32$) and less so with the other physical areas. Item 10 on lack of freedom correlated highly with COM, MOB, and ADL, and less so with EAT. All EMO items correlated highly with COM, except items 5 on being a burden and 9 on worries about future (**Table 8**).

At the third evaluation every EMO item maintained its high correlation with total EMO. The feelings with the highest correlations were items 4 on hopelessness ($r = 0.91$), 6 on keep going ($r = 0.84$), 2 on feeling bored ($r = 0.83$), and 8 on depression ($r = 0.80$). Item

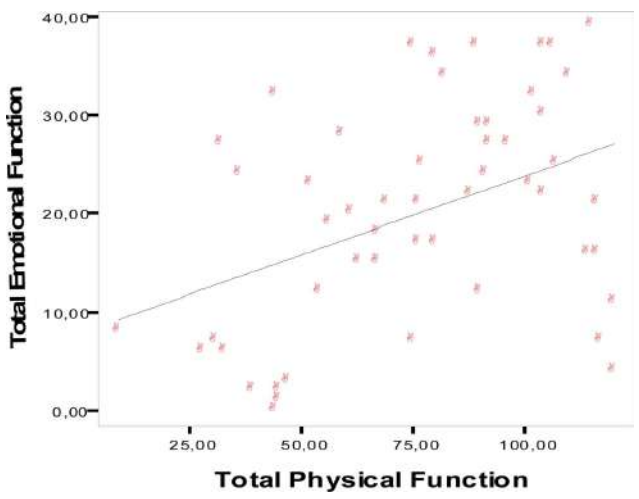

FIGURE 2 | Dispersion graph for emotional functioning and total combined physical functions at the third evaluation.

Table 4 | Correlations between areas at the first evaluation.

	ADL	EAT	COM	EMO
MOB	0.400**	0.001	−0.046	0.360**
ADL	1	0.095	0.017	0.242*
EAT		1	0.856**	0.307**
COM			1	0.398**

*$p < 0.05$ bilateral; **$p < 0.01$ bilateral.*

Table 5 | Correlation between areas at the second evaluation.

	ADL	EAT	COM	EMO
MOB	0.552**	0.022	0.165	0.331**
ADL		0.203	0.317**	0.346**
EAT		1	0.854**	0.342**
COM			1	0.444**

*$p < 0.05$ bilateral; **$p < 0.01$ bilateral.*

Table 6 | Correlation between areas at the third evaluation.

	ADL	EAT	COM	EMO
MOB	0.556**	0.278*	0.300*	0.330*
ADL	1	0.220	0.301*	0.267
EAT		1	0.845**	0.301*
COM			1	0.355**

*$p < 0.05$ bilateral; **$p < 0.01$ bilateral.*

Table 7 | Correlations between EMO items and other areas at the first evaluation.

EMO Items	MOB	ADL	EAT	COM	EMO
1. I have felt lonely	0.148	0.112	0.386**	0.399**	0.673**
2. I have felt bored	0.217*	0.183	0.249**	0.332**	0.625**
3. I have felt embarrassed in social situations	0.052	−0.011	0.433**	0.507**	0.540**
4. I have felt hopelessness about the future	0.294**	0.144	−0.049	0.017	0.670**
5. I have worried about being a burden to other people	0.265**	0.241*	0.087	0.133	0.702**
6. I have wondered why I keep going	0.274**	0.163	0.306**	0.290**	**0.740****
7. I have felt angry because of the disease	0.297**	0.272**	0.227*	0.293**	**0.751****
8. I have felt depressed	0.274**	0.214*	0.200*	0.254**	**0.812****
9. I have worried about how the disease will affect me in the future	0.198*	0.154	0.054	0.154	0.712**
10. I have felt as if I have no freedom	0.441**	0.197*	0.168	0.309**	0.688**

*$p < 0.05$ bilateral; **$p < 0.01$ bilateral.*

Bold indicates higher values that are most significant.

Table 8 | Correlations between EMO items and other areas at the second evaluation.

EMO Items	MOB	ADL	EAT	COM	EMO
1. I have felt lonely	0.081	0.106	0.416**	0.462**	0.620**
2. I have felt bored	0.253*	0.406**	0.351**	0.408**	0.757**
3. I have felt embarrassed in social situations	0.170	0.125	0.337**	0.371**	0.561**
4. I have felt hopelessness about the future	0.271*	0.260*	0.241*	0.324**	**0.847****
5. I have worried about being a burden to other people	0.216	0.289*	0.085	0.123	0.704**
6. I have wondered why I keep going	0.290*	0.252*	0.235*	0.295**	0.766**
7. I have felt angry because of the disease	0.290*	0.295**	0.223	0.334**	0.769**
8. I have felt depressed	0.254*	0.252*	0.181	0.326**	**0.844****
9. I have worried about how the disease will affect me in the future	0.088	0.066	0.118	0.162	0.658**
10. I have felt as if I have no freedom	0.477**	0.450**	0.256*	0.380**	**0.783****

**$p < 0.01$ bilateral; *$p < 0.05$ bilateral.*

Bold indicates higher values that are most significant.

Table 9 | Correlations between EM items and other areas at the third evaluation.

EMO Items	MOB	ADL	EAT	COM	EM
1. I have felt lonely	0.254	0.011	0.149	0.145	0.682**
2. I have felt bored	0.319*	0.163	0.364**	0.298*	**0.826****
3. I have felt embarrassed in social situations	0.164	0.174	0.255	0.317*	0.634**
4. I have felt hopelessness about the future	0.238	0.220	0.076	0.152	**0.913****
5. I have worried about being a burden to other people	0.234	0.286*	0.138	0.219	0.698**
6. I have wondered why I keep going	0.193	0.166	0.143	0.209	**0.836****
7. I have felt angry because of the disease	0.233	0.181	0.245	0.152	0.777**
8. I have felt depressed	0.370**	0.313*	0.339*	0.494**	**0.801****
9. I have worried about how the disease will affect me in the future	0.121	0.186	0.205	0.299*	0.762**
10. I have felt as if I have no freedom	0.425**	0.377**	0.433**	0.488**	0.764**

**$p < 0.01$ bilateral; *$p < 0.05$ bilateral.*

Bold indicates higher values that are most significant.

4 on hopelessness and item 6 on keep going did not correlate with any of the physical disabilities. Item 2 on boredom correlated highly with EAT and less so with MOB and COM. Item 8 on depression correlated highly with COM and MOB and less so with ADL. Item 10 on lack of freedom was highly correlated ($p < 0.01$) with the five areas (**Table 9**).

DISCUSSION

This study shows that as the physical deterioration of the patients with ALS increased, the self perception of the emotional distress remained more or less stable, and this happened in both spinal and bulbar onset patients, who have different timings of their physical disabilities. Emotional distress was felt, on average, as

intermediate between none or worst. At the first evaluation the most frequent worries, felt more than *sometimes* but less than *frequently*, were those about the future, of losing autonomy, of being a burden, and then of despair. Less frequently felt, just *sometimes*, were depression and anger, which were more frequently felt nearer the time of diagnosis. This pattern continued at the second evaluation, with a slight increase in loss of freedom and with depression felt slightly less than *sometimes*. At the last evaluation, between 18 and 24 months after diagnosis, the pattern continues but lack of autonomy is the prevalent feeling followed by fear of the future and of being a burden, these three feelings got closer to being felt *frequently*. Depression remained stable, just being felt *sometimes*.

This pattern suggests that, for Spanish patients attending an ALS unit, the most frequent distressful thoughts are those related to fear of the future and of loss of autonomy with concerns for loved ones. Feelings of hopelessness, of depression and anger were felt less often. This might be explained by the attendance of a specialized clinic whose professionals try to fight those negative feelings with constant information on research, clinical trials, and psychological surveillance. Other explanations could be linked to the patients´ shared cultural and social background.

All four physical disabilities correlate with EMO, but it is the COM disability that has the most emotional impact as soon as it appears. This implies that dedicated care of this disability is important since it is a cause of significant distress. On the whole, physical disabilities accounted for only 25–16% of the emotional distress, and less so as the disease advances. Other varied psychosocial factors may contribute to modify the EMO (Pagnini, 2012). However, each negative feeling tested correlated highly with the global emotional dysfunction. It seems plausible that any psychosocial factor, such as advanced health care, strong familial, and social support, spirituality, or an optimistic personality, could influence the EMO of the patient by changing their patterns of feelings or emotions. Negative thoughts, not the physical disabilities *per se*, may account for an important part of the emotional distress felt by patients. We have known for a long time that emotional distress does not depend on the physical damage that one experiences but on the way that the mind processes the experience (adapted from Epicurus, 300 B.C.: "*To humans, the things do not affect us by themselves, but by the way we interpret them*").

All 10 feelings or emotional states tested correlate strongly with the global EMO, but each one has a different weight as representative of the patient's EMO at different times. Less than 1 year after diagnosis depression is the feeling with most emotional impact, followed by anger, although on average they were felt only "*some times.*" Both are highly related to the dysfunctions in COM and MOB. Once most disabilities are present, 18 months after diagnosis, feelings of hopelessness reach the same power as depression, with the COM disabilities contributing most to these feelings. Two years after diagnosis, most feelings have increased their impact, but those of hopelessness and of stopping fighting are the most representative. Worries about the future and of lack of freedom are perceived often but produce a lesser impact. Interestingly, except for lack of freedom, none of the emotional states are related to the severity of the physical dysfunctions at this stage of the disease. In this way, they are negative states of mind, not directly related to the physical disabilities, and so, subject to be treated by dedicated psychotherapy.

Many studies have tried to determine what is called the QoL of patients with ALS, and many scales have been created that try to measure it. QoL may be a confusing concept in this dreadful disease, which makes it more difficult to "measure." The methodological limitations inherent to this measurement contribute to a wide range of reported results, and statements on QoL must be considered dependent of the scale used. An excellent review has recently been published (Pagnini, 2012). QoL has been reported to be negatively correlated to suffering, a sense of burden, and hopelessness, and positively correlated to social support (Epton et al., 2009). Its relation with physical functioning was unclear to some (Ganzini et al., 1999) and it was more related to psychosocial rather than physical aspects of life, particularly in those patients with physical disabilities (Clarke et al., 2001). QoL, as assessed by the patient, has not been correlated to physical function or strength, but to psychological and existential factors, as well as to spiritual factors and support systems (Simmons et al., 2000, 2006). Hopelessness in ALS has been correlated with suffering and negatively with QoL (Ganzini et al., 1999). Hope did not correlate with physical and respiratory functions (Fanos et al., 2008). The real prevalence of depressive and anxious symptom in ALS is unclear (Norris et al., 2010; Taylor et al., 2010) although some studies found depressive symptoms common, and severe in 11–15% of the patients (McLeod and Clarck, 2007). Swallowing and breathing difficulties have been related to depressive symptoms, however the severity of the disease as such or its duration were not (Hillemaker et al., 2004). Most of these studies are in accordance with our findings.

An evaluation of 28 studies concluded that clinically significant depression is neither as prevalent nor as severe as might be expected and that patients are more likely to present with hopelessness and end-of-life concerns than clinically significant depression (Averill et al., 2007), this is consistent with our findings. Thirty ALS patients showed good psychosocial adjustment and subjective QoL, mild depressive symptoms, and no clinically relevant depression (Lulé et al., 2012). Another study rated QoL on average as satisfactory and found a moderate positive relation to physical impairment and a weak negative relation to time since diagnosis (Kubler et al., 2005). Despite marked deterioration in the patients' health, there was no change in mental well-being and QoL. Psychological well-being appeared more important in maintaining QoL than physical factors (O'Doherty et al., 2010). Few changes were observed in the QoL of 35 patients over time (Olsson et al., 2010). The general QoL changed little overtime in 60 patients (Robbins et al., 2001). Individual QoL remained stable in 42 patients and was not dependant on physical function but on family, friends/social life, health, and profession (Neudert et al., 2004). There was substantial steadiness of QoL in 31 patients over 9 months (Gauthier et al., 2007). No relationship between EMO and muscle strength or functional ability was found in 30 patients (Palmieri et al., 2010). Most of these studies are in accordance with our findings.

What emerges from our study and others is that for ALS patients, as a group, physical dysfunction *per se* is not the main contributor to emotional suffering. Emotional suffering seems more related to negative feelings linked to the new physical condition. However, emotional dysfunction, and depression at its paradigm, do not seem to be exaggerated in spite of severe physical dysfunction and remain somehow stable along most of the disease. Terminal phases need additional studies. Since we do not agree with the idea of ALS affecting only nice and suffering-resilient people, we understand that ALS patients as a group behave as any other human group who try to cope with misfortune the best they can. As in any human disaster the emotional health of each ALS patient is not completely dependent on his/her physical strength but on the strength of the coping mechanisms that he/she may build to deal with the situation These mechanisms may be individual, familial, social, or spiritual, health care provided or other. It is difficult and risky to extrapolate results obtained from groups to individual patients since the individual variables that influence the specific QoL of each person are so varied. To facilitate the work of the therapists, our study tries to understand the contribution of specific negative feelings and worries, and their subsequent emotional states, to the emotional suffering of the patients throughout their disease, and which specific physical disabilities are most related to them. Specific psychotherapeutic interventions should be implemented to help the patient to overcome them. Development of adequate protocols is needed (Pagnini et al., 2012).

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Well-being in amyotrophic lateral sclerosis: a pilot experience sampling study

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Objective: The aim of this longitudinal study was to identify predictors of instantaneous well-being in patients with amyotrophic lateral sclerosis (ALS). Based on flow theory well-being was expected to be highest when perceived demands and perceived control were in balance, and that thinking about the past would be a risk factor for rumination which would in turn reduce well-being.

Methods: Using the experience sampling method, data on current activities, associated aspects of perceived demands, control, and well-being were collected from 10 patients with ALS three times a day for two weeks.

Results: Results show that perceived control was uniformly and positively associated with well-being, but that demands were only positively associated with well-being when they were perceived as controllable. Mediation analysis confirmed thinking about the past, but not thinking about the future, to be a risk factor for rumination and reduced well-being.

Discussion: Findings extend our knowledge of factors contributing to well-being in ALS as not only perceived control but also perceived demands can contribute to well-being. They further show that a focus on present experiences might contribute to increased well-being.

Keywords: amyotrophic lateral sclerosis, ALS, coping, well-being, experience sampling, ESM, reminiscence, rumination

1. INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a rare neurodegenerative disease characterized by progressive paralysis (Logroscino et al., 2008). In the absence of a cure (Logroscino et al., 2008, 2010) the treatment of ALS focuses on the alleviation of symptoms and the maintenance of the best possible degree of functioning (Clarke et al., 2001). A rich literature exists on factors influencing quality of life and coping with the disease (c.f. Pagnini, 2013). For example, different styles of coping (Matuz et al., 2010; Montel et al., 2012a), spirituality (McLeod and Clarke, 2007), or care-giver relations (Chiò et al., 2004) have all been related to psychosocial well-being in patients with ALS. In line with psychological theories on subjective quality of life (e.g., Rapkin and Schwartz, 2004) the great physical burden of ALS shows no simple relationship to well-being, with many studies showing small and insignificant correlations (Robbins et al., 2001; Pagnini, 2013) or even positive associations (Lulé et al., 2009). However, many of the questionnaires used in research on well-being and quality of life in patients with ALS require participants to generate aggregate statements about their experiences, e.g., by asking them how they felt (on average) during the past days (Cohen et al., 1995; Robbins et al., 2001) or even weeks (Hammer et al., 2008). Thus, little is known about the factors which are associated with instantaneous well-being, i.e., well-being as it fluctuates from moment to moment throughout the day.

In this study, therefore, the experience sampling method (ESM) was used (Larson and Csikszentmihalyi, 1983; Stone et al., 2003) to analyze possible predictors of well-being. Experience sampling, originally developed because of concerns of how accurate people are in "reconstructing their experience[s] after the fact" (Larson and Csikszentmihalyi, 1983, p. 42), asks participants to record their experiences directly at the moment of sampling. By randomizing sampling times throughout the study period, it is possible to collect representative data on the participants' experiences, such as well-being, and possible influencing factors (Shiffman et al., 2008; Scollon et al., 2009).

At its most basic level, flow theory assumes that the physical and mental activities people engage in, influence their well-being. More specifically, it predicts that well-being is highest if perceived control and perceived demands match in a given situation (Csikszentmihalyi, 1990). Any imbalance between demands and abilities results in reduced well-being, e.g., feelings of frustration, when demands exceed abilities, or of boredom, when abilities exceed situational demands (Csikszentmihalyi, 1990). Given that the progressive loss of motor functions requires constant adaptation and change (King et al., 2009), we hypothesized that

finding this balance would be of crucial importance in patients with ALS. A second prediction of flow theory is that well-being depends on the extent to which thoughts are focused on present experiences (Schmidt et al., 2007). However, the little data available from patients with ALS is heterogeneous. Support comes from a study by Plahuta et al. (2002), which found that hopelessness, a future oriented direction of thought, is related to increased suffering and higher intentions of suicide in patients with ALS. However, the use of the coping strategy "planning" (Carver, 1997), an arguably more direct and less negatively valenced indicator of "thoughts directed toward the future" does not seem to be strongly related to well-being (Montel et al., 2012b). Qualitative findings from interviews with patients are also mixed (Fanos et al., 2008). On the one hand, several subjects indicated the use of "living in the moment" as a successful coping strategy while others sought consolation in remembering positive past experiences. The constant adaptation and change required for coping with ALS (King et al., 2009), necessitates disengaging from goals no longer attainable, or anticipating disengagement from goals which may become unattainable in the future. Generally, confrontation with unattainable goals—even more so when the factors which make a goal unattainable are essentially uncontrollable as is the case in ALS (Nolen-Hoeksema et al., 2008)—has been shown to be a risk factor for rumination, and, thus, decreased well-being (Nolen-Hoeksema, 1991; Martin and Tesser, 1996). Therefore, we hypothesized that thinking about the past and future would be associated with reduced well-being, and that rumination would mediate this effect.

2. METHODS

2.1. PATIENTS

A convenience sample of ten patients (seven male; see **Table 1**) fulfilling the revised El Escorial criteria for clinically definite ALS (Brooks et al., 2000) was recruited via the Institute for Medical Psychology and Behavioral Neurobiology of the University of Tübingen and the Department of Neurology of the University of Ulm. All participants contacted for inclusion agreed to participate in this study. Mean time since diagnosis was 38.10 months ($SD = 35.96$, range = 12–129). One patient had a percutaneous endoscopic gastrostomy (PEG), and three were non-invasively ventilated. The study was approved by the Ethical Review Board of the Medical Faculty, University of Tübingen. Written informed consent was obtained from all participants.

Table 1 | Patients' Characteristics.

	ALSFRS-R	ADI-12	well-being	*M*	*SD*	Range
Age (years)	0.52	0.32	−0.09	52.30	11.56	35–71
ALSFRS-R		0.59$^{\#}$	−0.75*	19.20	10.57	1–35
ADI-12			−0.63$^{\#}$	20.70	7.41	12–34
well-being				4.79	0.69	3.93–5.86

Intercorrelations, means, and standard correlations.
Note: $N = 10$. $^{\#}p < 0.10$, $^{*}p < 0.05$.

2.2. PROCEDURE

We collected data on well-being, perceived demands, perceived control, temporal direction of thoughts and rumination over the course of two weeks at three randomly chosen times per day using the ESM. Patients were provided with a pager that beeped when they should record their experiences using a standardized questionnaire. To avoid interference with morning and evening caring routines, sampling was restricted to between 10 a.m. and 6 p.m. Patients were instructed to answer the ESM-questionnaires immediately after the beep and while answering the questions to refer only to the situation in which the beep occurred. At the beginning of the two weeks study period, patients were visited at their homes and the procedure was explained in full detail and questions concerning the study protocol were answered.

2.3. MEASURES

Functional status was assessed with the revised ALS Functional Rating Scale (ALSFRS-R) (Cedarbaum et al., 1999), and the extent of depressive symptoms with the ALS specific ALS Depression Inventory (ADI-12) (Hammer et al., 2008). These standardized measures were collected once at the beginning of the two week study period.

The ESM-questionnaire used in this study was previously used by Csikszentmihalyi and Larson (1987) and assessed the extent of perceived demands and control with two items, "How challenging was your activity?" and "Was the situation under your control?" To minimize participants' burden in terms of time and effort, rumination was measured with the single item "Did your thoughts turn round in circles?" (Jong-Meyer et al., 2009) and temporal direction of thoughts with two face-valid items ("Did you look ahead/to the past?"). Each item was scored on a 10-point Likert-type scale ranging from 0 (low) to 9 (high). Patients' well-being was measured with 13 well-being-related items developed by Larson and Csikszentmihalyi (1983). Each item was scored on a 7-point Likert-type scale, and a composite score reflecting well-being was derived by averaging ESM-items of the well-being category. To determine the reliability of this scale while taking the inter-correlation of repeated measurements into account Cronbach's α was calculated across subjects for every time point during the 2-week study period, yielding 42 coefficients. Reliability of the well-being scale was satisfactory (median $\alpha = 0.86$).

Patients completed an average of 33.30 assessments (range 13–43). Fifty percent of all questionnaires were answered within 10 min and 75% within 45 min after the beep. Further analysis revealed that without the most disabled participant (one male who used a personal computer to answer the questionnaires) 75% of all questionnaires were answered within 30 min after the beep. One patient was excluded from the following analyses because of excessive numbers of missing items, leading to a final sample size of $N = 9$.

2.4. STATISTICAL ANALYSES

Random intercept multiple regression analysis was used to test the hypothesis that well-being depended on the balance of demands and control (Edwards and Cooper, 1990; Edwards, 1994, also see Supplementary Material). The analysis was also performed with

functional status included as a covariate, which indicated that the results we report here were independent of functional status. Mediation analysis (MacKinnon et al., 2002; Kenny et al., 2003) was used to test the hypothesis that thinking about the past would have a negative effect on well-being and that this effect would be mediated by rumination. We report 95% confidence intervals for the mediated effect (Tofighi and MacKinnon, 2011). The same analysis was repeated for thinking about the future. Analyses were performed in R (R Development Core Team, 2011). Cohen's f^2 was calculated as a measure of the effect size (Selya et al., 2012).

3. RESULTS

Average well-being (see **Table 1**) was marginally negatively associated with symptoms of depression, but significantly positively associated with functional status. Functional status was marginally positively associated with symptoms of depression. Patient's age was not associated with functional status, symptoms of depression, or well-being.

Our first hypothesis suggested that well-being would depend on the balance of perceived control and demands. However, no support was found for this prediction (see Supplementary Material). Instead, results indicated that perceived control was associated with increased well-being ($b = 0.18$, $SE = 0.03$, $p < 0.001$, $f^2 = 0.22$), regardless of the level of perceived demands. In contrast, the effect of perceived demands depended on whether these demands were perceived as *controllable*, they were associated with increased well-being ($b = 0.09$, $SE = 0.02$, $p < 0.001$, $f^2 = 0.17$). If demands were perceived as *uncontrollable*, the positive effect of demands was significantly reduced ($b = -0.14$, $SE = 0.05$, $p < 0.01$, $f^2 = 0.03$), rendering the effect of demands on well-being non-significant ($b = 0.02$, $SE = 0.05$, $p > 0.70$, $f^2 = 0.01$).

Our second hypothesis proposed that thinking about the past would lead to increased rumination which in turn would reduce well-being. **Table 2** shows that thinking about the past (Row 1), thinking about the future (Row 2), and rumination (Row 3) were associated with lower well-being, and that thinking about the past (Row 4) was significantly and thinking about the future (Row 5) was marginally associated with higher rumination. Mediation analysis confirmed a negative effect of thinking about the past on well-being via rumination ($b = -0.03$, 95% CI [−0.05 −0.02]). No evidence was found that the negative effect of thinking about the future on well-being was mediated via increased rumination ($b = -0.01$, 95% CI [−0.02 0.001]).

4. DISCUSSION

Little is known about how patients with ALS cope with their disease from moment to moment in daily life. Thus, in this study the ESM was used to record patients' experiences throughout the day. Despite their severe physical disability, patients were able to complete the ESM-questionnaires within a short time after the scheduled signal. These results provide evidence that even a potentially demanding procedure such as the ESM may be a valuable tool in assessing patients' thoughts, well-being and cognitive state. The relationships between functional status, presence of depressive symptoms and well-being indicated that depressive symptoms were more present and well-being was lower in early stages of the disease. This result mirrors findings of better quality of life in patients who are longer affected by the disease (Lulé et al., 2008, 2009).

Flow theory predicts that well-being depends on finding the optimal balance between perceived demands and control (Csikszentmihalyi, 1990), and we hypothesized that finding this balance would be of crucial importance in patients with ALS. However, our data did not support this hypothesis. Instead, but in line with previous findings (Plahuta et al., 2002), perceived control was associated with increased well-being, regardless of the level of perceived demands. However, our results extend this idea, by showing that increased demands can also contribute to increased well-being, as long as they are perceived as controllable. While flow theory is primarily concerned with experiences related to activities in the present, experiences may also differ in their temporal orientation. We hypothesized that if attention is not focused on the here and now, but directed toward the past or the future, this would increase the risk for rumination, which in turn would reduce well-being. Our results indicate that thinking about the past was indeed associated with decreased well-being and that this effect was mediated by rumination. While some patients may find solace in remembering the good times they have had (Fanos

Table 2 | Results of mediation analysis.

	Predicted	Predictor	*b*	*SE*	*DF*	*t*	*p*	f^2
PREDICTORS OF WELL-BEING								
1	Well-being	Thinking about the past	−0.03	0.01	250.83	−2.73	0.01	0.02
2	Well-being	Thinking about the future	−0.03	0.01	250.97	−2.08	0.04	0.01
3	Well-being	Rumination	−0.08	0.01	255.84	−5.60	<0.001	0.10
PREDICTORS OF RUMINATION								
4	Rumination	Thinking about the past	0.41	0.04	252.89	10.34	<0.001	0.40
5	Rumination	Thinking about the future	0.09	0.05	252.50	1.70	0.09	0.01
MEDIATION MODELS								
6	Well-being	Thinking about the past	0.00	0.01	247.77	0.17	0.87	
7		Rumination	−0.08	0.02	254.12	−4.79	<0.001	
8	Well-being	Thinking about the future	−0.02	0.01	250.30	−1.66	0.10	
9		Rumination	−0.08	0.01	254.83	−5.43	<0.001	

et al., 2008), reminiscing may also introduce the risk of being reminded of unattainable goals, thus, in turn, increasing the risk of reduced well-being. Likewise, thinking about the future was negatively associated with well-being; however, it was only loosely related to rumination, and no support was found for rumination mediating a negative effect of thinking about the future on well-being. We may thus speculate that thoughts about the future are not necessarily ruminative, possibly only in patients experiencing hopelessness (Plahuta et al., 2002).

4.1. LIMITATIONS AND CONSIDERATIONS FOR FUTURE STUDIES

4.1.1. Sampling

Several limiting factors of the current study deserve attention. To minimize interruption of daily routine, time slots in which patients had pre-set appointments (e.g., occupational therapy) were excluded from the experience sampling and sampling was restricted to the time between 10 a.m. and 6 p.m. This restriction may have prevented us from sampling several activities of daily living, e.g., personal hygiene, which may be very demanding and frustrating for severely ill patients (Foley et al., 2014).

4.1.2. Economic considerations

From a research perspective it is often desirable to use longer rather than shorter instruments, if only to increase reliability (Spearman, 1910). However, in a repeated measures context, this desire needs to be balanced with economic considerations, especially in a sample in which motor difficulties, e.g., when holding a pen, are common. Thus, to avoid spurious results, e.g., low well-being due to the frustrating experience of having to repeatedly answer a long questionnaire, and to reduce the risk of high levels of non-reponse (Iglesias and Torgerson, 2000) the questionnaires we used were kept as short as possible. Yet it is clear, that assessing rumination with only one item is a simplification of a complex construct. However, both empirical (Jong-Meyer et al., 2009) as well as theoretical accounts (Carver, 1996) suggest, that the item we used possesses high face validity for assessing rumination.

4.1.3. Sample size and generalizability

Finally, although not uncommon in ESM studies (e.g., Teuchmann et al., 1999), the small sample size limits generalization of results, until future studies can replicate our findings. Further, our analyses focused on within-subject variables, but between-subject factors and their interactions could also play an important role. For example, care-givers tend to underestimate the patient's quality of life (Trail et al., 2003), and it might be interesting to know, whether this is accompanied by a tendency to shield the patient from demanding activities, which according to our findings, might actually improve the patient's well-being. To the best of our knowledge, our study is the first to employ the ESM in patients with ALS. Thus, little information on appropriate sample sizes was available beforehand, demonstrating the pilot character of this study. Judging from the obtained effect sizes, mainly small to medium according to Cohen (1992), we suggest increasing sample sizes in future studies. Results from simulation studies (Snijders and Bosker, 1993) suggest, that an increase in the number of participants might be of greater interest than increasing the number of observations per participant. Further, if a research question focused primarily on between-subject factors (see above) a larger sample size would also be recommended. Thus, it should be kept in mind, that the optimal balance between number of participants and the number of observations per participant is dependent on the particular research question.

The ESM methodology has been applied in a variety of chronic diseases, e.g., in patients with cancer, chronic pain, cardiovascular diseases, or patients requiring hemodialysis (c.f. Smyth and Stone, 2003), testifying to the wide applicability of the method (c.f. Christensen et al., 2003). However, depending on the research questions, sophisticated data analysis methods, and technical equipment, e.g., electronic paging and recording devices with a user-friendly and unobstrusive interface, may be needed. Given the large challenge of living with ever progressing motor impairments, we suggest that future studies may take full advantage of the widespread availability of smartphones which lend themselves to ESM-studies (e.g., Runyan et al., 2013). Using such a system it might even become possible to densely track the evolution of coping with ALS over prolonged periods of time. However, apart from generating valuable data for research purposes, such a procedure might also affect patients' well-being, e.g., by making relations between certain situations and well-being transparent to the patient.

4.2. SUMMARY

Our results suggest that the ESM may be a valuable tool to elucidate components of coping and well-being in daily life in patients with ALS. Perceived control over challenging situations seems to be of major importance for maintaining high well-being. We further show that well-being may not only depend on perceived control, but that it also depends on the level of perceived demands. Encouraging patients to pursue, within limits, potentially demanding activities might help to improve their well-being.

Both thoughts directed toward the past and the future may negatively affect well-being, whereas rumination mediates this effect when thoughts are directed toward the past. We speculate that patients who experience poor well-being and may even be depressed might benefit from interventions which not only strengthen an internal locus of control (Nonnenmacher et al., 2013; Foley et al., 2014) but also encourage living in the present.

On a more global perspective the flow-theoretical approach and our results correspond well with recent work aiming at evaluating mindfulness-based (Kocovski et al., 2009) interventions in patients with ALS (Pagnini et al., 2014a,b). These interventions aim to help focusing on the experiences in the here and now, and thus to reduce the risk of reactive, e.g., ruminative, thoughts, which may otherwise reduce well-being or even lead to depression (Bishop et al., 2004). Our results provide further evidence for this promising approach, by highlighting the importance of the temporal direction of thoughts and the importance of perceived demands and control for the experience of well-being in patients with ALS.

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SUPPLEMENTARY MATERIAL

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Impact on children of a parent with ALS: a case-control study

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Background: Numerous studies have explored how patients and their caregivers cope with amyotrophic lateral sclerosis (ALS), but the literature completely lacks research on the psychological impact of the disease on patients' children. The aim of our study was to investigate the emotional and psychological impact of a parent with ALS on school-age children and adolescents in terms of problem behavior, adjustment, and personality characteristics.

Methods: The study involved 23 children (mean age = 10.62 years, six females) with a parent suffering from ALS, and both their parents. Children were matched for age, gender, and birth-order with a control group of children with healthy parents. They were administered the Youth Self Report (YSR) questionnaire and the Rorschach Comprehensive System, and their healthy parent completed the Child Behavior Checklist (CBCL).

Results: Findings clearly showed that, compared with controls, children with a parent who had ALS had several clinically significant adverse emotional and behavioral consequences, with emotional and behavioral problems, internalizing problems, anxiety and depressive symptoms. Children of a parent with ALS scored higher than controls for the Total Problems, Internalizing Problems, Anxious/Depressed and Withdrawn/Depressed scales in the YSR. A relevant percentage of children fell within the clinical range (42.9%) and borderline range (28.6%) for Internalizing Problems. The Rorschach CS confirmed the substantial impact of ALS in a parent on their offspring in terms of internalizing behavior and depression, with adjustment difficulties, psychological pain, and thought problems.

Conclusion: Our findings indicate that school-aged children and adolescents with a parent who has ALS are vulnerable and carry a substantially higher risk of internalizing behavior, depressive symptoms, and reactive problems than children with healthy parents. Families affected may need support to cope with such an overwhelming disease.

Keywords: ALS, chronic medical condition (CMC), parents-children, problem behavior, Rorschach

Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative disease involving both upper and lower motor neurons, and leading relentlessly to progressive muscle atrophy and weakness, dysphagia and dysarthria. In most cases, patients die within 3–5 years of the disease's onset, usually due to respiratory failure (Rowland and Shneider, 2001). Secondary symptoms that often affect patients and, indirectly, their caregivers in everyday life are pain (Pagnini et al., 2011), emotional lability (Palmieri et al., 2009), and sleep disturbance (Blackhall, 2012).

There is no effective cure for ALS, so medical treatment is focused on physical symptom management (Aoun et al., 2012). The impact of the disease on patients can be huge, particularly on the early stage after diagnosis, often causing anxiety, depression, anguish, and suicidal ideation (Palmieri et al., 2010; Pagnini et al., 2012).

Amyotrophic lateral sclerosis is overwhelming and challenging for caregivers and families as well. When Cipolletta and Amicucci (2014) interviewed members of the families of ALS patients who had died, they found that the disease was perceived as a death sentence for the patient on the one hand, and as a family illness on the other. The authors concluded that ALS produces both centrifugal and centripetal adjustment processes (i.e., creating a greater distance between some family members, but bringing others closer together) and has several profound consequences on everyday family life.

Patients with ALS have to cope with serious restrictions and changes in their daily life. They need assistance with eating and dressing, nursing care, and mobility, that is often provided by a family member, and the patient's partner in nearly 80% of cases (Miller et al., 2000). The progressive nature of the disease gradually increases the patient's dependence on the primary caregiver, who may sometimes spend more than 11 h a day with the patient (Krivickas et al., 1997). Family caregivers of ALS patients are deeply affected by the illness and often experience burden due to physical strain, emotional tension, personal and social limitations (Rabkin et al., 2000), anxiety and depression (Chiò et al., 2005; Pagnini et al., 2012). Significantly, such symptomatic expressions in caregivers are reportedly connected with the patients' gradual loss of physical function (Gauthier et al., 2007; Pagnini et al., 2010).

Although many studies have explored how patients and their caregivers cope with ALS, the literature completely lacks any research on the specific psychological impact of such a devastating disease on the patients' children. It is important to investigate this issue in the case of ALS because the consequences of a parent's severe illness on their offspring can sometimes be dramatic, as already reported for a variety of diseases. In particular, the impact on children of a parent suffering from a chronic medical condition (CMC), i.e., a disease lasting at least 3 months and involving one or more apparata (Brown, 2006), such as cancer, HIV/AIDS, multiple sclerosis (MS), rheumatoid arthritis, brain damage, as well as others, has been well investigated.

According to the extant literature, a CMC in a parent involves the whole family and has a great impact on the parent's children (Visser-Meily et al., 2005). Long-term behavioral problems have been described in such children (van de Port et al., 2007), and their consequences have been seen to continue for several years after the parent's death (Wong et al., 2009). To give an example, Wong et al. (2009) examined the long-term impact of the childhood experience of a parent suffering from cancer and found that 44% of the individuals involved reported post-traumatic growth experiences in adulthood, while 59% reported experiencing adverse consequences, such as feelings of loss and void, concern for own health, negative changes in outlook on life, and negative impact on personal relationships.

More in general, children of an ill parent were reported to experience high levels of stress and to be at higher risk of health-related and social-emotional problems, such as somatic complaints, social isolation, excessive concern about becoming ill themselves, anxiety, depressive affects, and low self-esteem (Compas et al., 1994; Earley and Cushway, 2002; Faulkner and Davey, 2002; Ivarsson et al., 2002; Pedersen and Revenson, 2005; Flahault and Sultan, 2010; Sieh et al., 2010). A meta-analysis conducted by Sieh et al. (2010) showed that children growing up with a chronically ill parent were significantly more likely to have problem behavior than children of healthy parents. They were particularly at risk of internalizing behavior (anxiety, depression and withdrawal, and somatic complaints), but there was also evidence of more externalizing problems (aggressive and rule-breaking behavior) in the children with a chronically ill parent.

Among the studies on children with parents suffering from neurological CMCs, the case of MS has been the most thoroughly investigated (Arnaud, 1959; Blackford, 1992; Cross and Rintell, 1999; Steck et al., 2005; Diareme et al., 2006; Pakenham and Bursnall, 2006; Coles et al., 2007; Kalb, 2007; Steck et al., 2007; Yahav et al., 2007; Ehrensperger et al., 2008; Pakenham and Cox, 2008; Bogosian et al., 2010; Morley et al., 2011; Razaz et al., 2014). These studies have highlighted the strong impact of a parent with neurological disease on a child's psychological adaptation. Some recurrent developmental outcomes were identified, such as high levels of depression, anxiety, and low self-esteem, with changing roles, a heightened sense of responsibility and internalizing disorders.

Given these premises, the present study had three main objectives. First, we aimed to verify whether school-age children and adolescents who have a parent with ALS are more at risk of problem behavior, as measured by self-report questionnaires, than children of healthy parents. Consistently with the extant literature on CMCs in parents, we expected children with a parent who had ALS to display more internalizing and/or externalizing problems than controls. Second, we aimed to explore the psychological adjustment of children with a parent suffering from ALS by administering a performance-based task, the Rorschach test, scored using the Comprehensive System (CS; Exner, 2003; Exner and Edberg, 2005). Like Flahault and Sultan (2010), who used the Rorschach CS to examine how children adapted to having a parent with cancer as opposed to other illnesses, we aimed to integrate the information deriving from self-report questionnaires with a performance-based task. The Rorschach CS is a validated and reliable performance-based task that generates information of which the subject being tested

may be unaware (Flahault and Sultan, 2010). The third aim of the study was to explore how parents perceived their children's behavior and competences. In particular, we wanted to test the consistency and agreement between the parents' and their children's reported internalizing and externalizing problem behavior. The purpose to investigate the agreement among parents and children originates from the fact that previous research has shown that parents may underreport the problems of their children (Sourander et al., 1999). The demands and difficulties of the disease may make it arduous for a parent to recognize the needs of the children and to provide reliable information about their psychological functioning. The presence of discrepancies between parent and children reports may have some important implications for clinical practice. If children report more problems than parents do, it is likely that some of them do not receive appropriate psychological help because their difficulties remain unnoticed by adults (Sourander et al., 1999).

Materials and Methods

Participants

The study group consisted of 23 children with a parent suffering from ALS. The mean age of the children was 10.62 years ($SD = 3.98$ years, range: 5–17 years), six were females (26.1%), 17 were male (73.9%). The children belonged to 12 families in which one parent had ALS and the healthy spouse was the patient's main caregiver. The ill parent was the mother in five families, the father in seven.

Twenty-three children matched with the study group for age, gender, and birth-order formed a control group. They were recruited from the general population of children attending primary or secondary schools in the same area as the study group.

All participants were Caucasian and none of their parents were single. The participants' demographic details are shown in **Table 1**.

TABLE 1 | Demographic characteristics of the study sample and control group.

Parents' characteristics		
	Ill parent (n = 12)	**Spouse (n = 12)**
Mothers (*n,* %)	5 (41.7%)	7 (58.3%)
Fathers (*n,* %)	7 (58.3%)	5 (41.7%)
Age (mean, SD)	45.12 (6.5)	42.75 (3.2)
Age range (years)	31.5–52.5	38.0–47.7
Duration of illness, years (mean, SD)	6.93 (4.2)	
ALSFRS (mean, SD)	26 (8.4)	
Limb onset (*n,* %)	11 (91.7%)	
Bulbar onset (*n,* %)	1 (8.3%)	
Children's characteristics		
	Study group (n = 23)	**Control group (n = 23)**
Gender (*n,* %)		
Female	6 (26.1%)	6 (26.1%)
Male	17 (73.9%)	17 (73.9%)
Age (mean, SD)	10.62 (4.0)	10.74 (3.9)
Age range (years)	5.0–17.6	5.0–17.5
Number of children participating in the study per family (*n,* percent)		
1	5 (41.7%)	18 (90%)
2	3 (25%)	1 (5%)
3	4 (33.3%)	1 (5%)

ALSFRS, Amyotrophic lateral sclerosis functional rating scale.

Instruments and Measures

Children's Emotional/Behavioral Problems and Competences

Children aged 11 years and over ($n = 28$) were administered the Youth Self Report (YSR; Achenbach and Rescorla, 2001) and, for all the children the healthy parent completed the Child Behavior Checklist (CBCL; Achenbach and Rescorla, 2001).

The YSR is a self-administered questionnaire, part of the Achenbach System of Empirically Based Assessments (ASEBAs; Achenbach and Rescorla, 2001), developed to assess emotional and behavioral problems in children and adolescents between the ages of 11 and 18 years. The YSR includes 118 items rated on a 3-point scale ranging from 0 (not true) to 2 (very true). The instrument provides measures for Internalizing, Externalizing, and Total Problems, and eight syndrome scales, designated as Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior, with higher scores indicating more severe symptoms. The YSR also yields a measure of social competences, the Total Competence scale (comprising the Activities, Social, and School subscales), that assesses the amount and quality of the youth's involvement in sports, organizations, jobs and chores, social relationships, and school performance.

The CBCL is a rating scale, also part of the ASEBA, and it is the parallel form of the YSR for parents. It provides parent-reported information on a broad range of emotional and behavioral difficulties in a child during the previous 6 months. Like the YSR, the CBCL includes 118 items for measuring the eight syndrome scales and the three general dimensions of Internalizing, Externalizing, and Total Problems, plus 20 competence items (referring to the child's participation in hobbies, games, sports, jobs, chores, friendship, and activities).

As recommended by Achenbach and Rescorla (2001), we used raw scores for all comparisons involving the YSR and CBCL scores to take the full range of variation in these scales into account. The scores for Internalizing, Externalizing, and Total Problems were also converted into *T* scores to ascertain clinical, borderline, and normal ranges: *T* score below 60 = normal; between 60 and 63 = borderline; and 64 or above = clinical (Achenbach and Rescorla, 2001).

The CBCL and the Teacher's Report Form in the ASEBA have shown good validity and reliability characteristics in the Italian population (Frigerio et al., 2004).

Personality Characteristics

The children's personality characteristics were assessed using the Rorschach test, a performance-based task consisting of 10 official inkblots (five made with black ink on a white background, two with black and red ink on a white background, and three with multicolored ink on a white background). Forty-five Rorschach protocols were collected because one child in the study group refused to complete the Rorschach task. Exner's CS was used to administer and interpret the Rorschach protocols (Exner, 2003; Exner and Edberg, 2005), and the 'Structural Summary' of the scores was produced using the ROR-SCAN software (Caracena, 2002). The Rorschach CS protocols were scored by two experienced clinical psychologists because it has been demonstrated that training and experience with administering and scoring this type of task can have a major effect on CS scores (Lis et al., 2007). The Rorschach CS has standardized procedures, a high inter-scorer reliability, adequate test–retest reliability and validity, and reference norms based on large samples of normative or pathological respondents (Weiner and Exner, 1991; Weiner, 2000).

To obtain inter-scorer reliability, 10 protocols set were selected at random and scored independently by the two judges. Inter-scorer reliability was calculated by percentage of agreement and iota for 10 response segments. Iota is chance-corrected reliability coefficient that is equivalent to Cohen's kappa for a multivariable test scored by two or more raters (Janson, 2003, 2004). The percentages of agreement and iota values for response segments indicated satisfactory inter-scorer reliability (**Table 2**).

To prevent chance findings arising from multiple comparisons, we restricted the Rorschach variables analyzed in this study (Weiner, 1995), as in the method used by Flahault and Sultan (2010). Among the clusters belonging to the Structural Summary (Control and Management of Stress, Affects, Self-Perception, Interpersonal Relationships, Processing, Mediation, Ideation, and Psychopathological Constellations), we selected the Rorschach variables that had proved to be reliable markers of self-perception, affect modulation, individual adjustment, cognitive style, interpersonal functioning, emotional distress, anxiety, and depression (Weiner, 1998; Exner, 2003). As in Flahault and Sultan (2010), self-esteem was operationalized using the EGO index (reflection and pair responses); desirable self-image or pleasure in interaction with others using the GHR responses (Good Human Responses); physical preoccupations using the An + Xy contents (anatomy and radiography); emotional distress with the D score (tolerance of stress, control); anxiety and affects due to stress with the SumY (shading-diffusion) and m (object movement); and negative thoughts about the self and the world with the Vista (shading-vista), MOR (morbid content), SumC' (achromatic color), and DEPI (depression index) variables.

Several indexes were used to assess respondents' ideational processes and cognitive resources, namely variables regarding reality testing (X−%, distorted form; X+%, conventional form; XA%, very good form quality percent; Xu%, usual form), and variables regarding thought problems (i.e., Sum6, Number of Special Score; WSum6, Weighted Sum of Special Score; Level 2, Raw Number of Lv2 Special Score). We also used the intellectualizing index (2AB + [Art + Ay]) to examine variables that might reflect defensive mechanisms, such as the tendency to take refuge in fantasy (Ma/Mp), or to minimize emotional experiences. All these variables were analyzed as frequencies (considering the number of responses), and/or as categories when the frequency exceeded a cutoff validated in the CS.

Finally, we analyzed the Psychopathological Constellation indexes. When positive, these indexes point to the presence of depressive symptoms (DEPI), the risk of suicidal behavior (S-CON, Suicide Constellation), inadequate coping abilities (CDI, Coping Deficit Index), obsessive cognitive processing (OBS, Obsessive Style Index), paranoid thoughts (HVI, Hypervigilance Index), and thought disturbance (PTI, Perceptual Thinking Index).

TABLE 2 | Rorschach inter-scorer agreement on coding segments.

Variable	% Agreement	Iota (Kappa)
Whole responses	0.975	0.793
Location and space (two variables)	0.954	0.895
DQ (+, o, v/+, v)	0.894	0.732
Determinants (11 variables)	0.978	0.835
FQ (None, +, o, u, −)	0.673	0.512
Pairs	0.954	0.895
Contents (27 variables)	0.987	0.830
P	0.954	0.795
Z score	0.899	0.825
CS special scores (14 variables)	0.989	0.587

Procedure

Patients with possible, probable, or definite ALS – according to the El Escorial criteria for its clinical diagnosis (Ross et al., 1998; Brooks et al., 2000) – and their families were recruited through the Neurosciences Department of the University of Padova and the Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences of the Second University of Naples (SUN). All ALS patients recruited in our study were living at home with their families. A psychotherapist, experienced with ALS, informed both patients and their caregivers about the purposes of the study by telephone. Patients who agreed to participate were included in an experimental protocol that involved a home visit, during which a clinical psychologist trained in the use of the Rorschach CS administered the various tools to the patient's children and healthy spouse. Each home visit took ∼90 min. The study was approved by the Ethics Committee of Padova University. Written informed consent was obtained from all parents participating in the study.

Data Analysis

We compared the study and control groups for the measures derived from the YSR, CBCL, and Rorschach CS, using the non-parametric statistic of the Mann–Whitney *U* test for continuous variables and Pearson's chi square for categorical variables. The Mann–Whitney *U* test was preferred to other parametric statistics because non-parametric tests require few if

any assumptions about the shapes of the underlying population distributions and are more robust with small sample size (Siegel and Castellan, 1988). The criterion adopted for statistical significance was $\alpha = 0.05$ (two-tailed exact significance) and the effect sizes of differences were calculated as Cohen's (1988) *d* and classified, according to Cohen's guidelines, as small ($d = 0.20$), medium ($d = 0.50$), or large ($d = 0.80$). Cohen's *d* values of 1.30 and above were classed as very large (Sullivan and Feinn, 2012).

To check the consistency between the YSR completed by the children in the study group and the CBCL completed by their parents, we used Pearson's product–moment correlations to assess relative agreement (*T*-scores), and intraclass correlation coefficients (ICCs) to assess pairwise agreement between informants (absolute agreement). Pearson's correlation coefficient indicates a poor agreement when lower than 0.30, a moderate agreement between 0.30 and 0.50, and a good agreement when higher than 0.50 (Cohen, 1988). An ICC suggests poor agreement below 0.40, moderate to good agreement between 0.40 and 0.75, and excellent agreement above 0.75 (Novella et al., 2001). Wilcoxon Signed Ranks Tests were conducted to assess differences in the mean *T* scores obtained by the children in the study group and their healthy parents.

Results

Children's Emotional/Behavioral Problems and Competences

First we examined whether the children with a parent who had ALS differed from the controls in terms of emotional and behavioral problems and competences, as measured by the YSR ($n = 28$). The study group scored significantly higher than the control group for: Anxious/Depressed ($U = 35.0$, $z = -2.92$, $p = 0.003$), Withdrawn/Depressed ($U = 41.0$, $z = -2.65$, $p = 0.007$), Internalizing ($U = 31.0$, $z = -3.08$, $p = 0.001$), and Total Problems ($U = 41.0$, $z = -2.62$, $p = 0.008$). The differences for Aggressive Behavior ($U = 58.5$, $z = -1.84$, $p = 0.066$) neared statistical significance, while no differences emerged for Externalizing Problems or any of the other syndrome and social competence scales (**Table 3**). The effect sizes relating to the scales with significant differences were large ($d > 0.8$), and for Internalizing Problems Cohen's *d* was very large (>1.30; Sullivan and Feinn, 2012).

Analyzing the scores for Internalizing, Externalizing, and Total Problems in terms of their clinical relevance, we found 6 (42.9%) of 14 children with a parent who had ALS were in the clinical range on the Internalizing scale, 4 (28.6%) were borderline, and only 4 (28.6%) were in the normal range. Conversely, none of the 14 children in the control group was in the clinical range, 2 were borderline, and 12 were in the normal range. The difference between the two groups was statistically significant (χ^2 $[2, N = 28] = 10.67$, $p = 0.004$).

No such differences emerged between the groups in terms of their distribution in the Externalizing (χ^2 $[2, N = 28] = 3.04$, *ns*), and Total problem (χ^2 $[2, N = 28] = 4.17$, *ns*) scales.

Children's Personality Characteristics

The personality characteristics (derived from the Rorschach CS) of the children in the two groups were compared using the Mann–Whitney *U* test and chi-square statistics: the statistically significant results are presented in **Tables 4** and **5,** respectively.

The children with a parent suffering from ALS had several variables that, interpreted in accordance with the CS, were indicative of a less adequate psychological functioning than the children in the control group. They showed signs of more self-disgust, shame, emotional distress, and guilt (SumV, SumV > 0), more

TABLE 3 | Comparison of emotional and behavioral problems and competences (YSR) between children with and without a parent suffering from ALS.

	Study group ($N = 14$)		Control group ($N = 14$)					Cohen's *d*
Scale	***M***	**SD**	***M***	**SD**	***U***	***z***	***P***	
Anxious/Depressed	8.86	3.30	5.00	2.88	35.0	−2.92	0.003**	1.25
Withdrawn/Depressed	4.43	2.34	2.14	1.70	41.0	−2.65	0.007**	1.12
Somatic Complaints	4.50	4.16	2.79	1.67	81.0	−0.79	0.442	0.54
Social Problems	4.50	2.95	2.86	2.14	64.0	−1.58	0.119	0.64
Thought Problems	3.57	3.32	1.86	1.41	67.5	−1.43	0.158	0.67
Attention Problems	6.36	3.52	4.64	1.98	78.0	−0.93	0.364	0.60
Rule-Breaking Behavior	2.00	0.88	2.36	2.90	80.5	−0.822	0.423	−0.17
Aggressive Behavior	8.07	3.73	5.64	3.10	58.5	−1.84	0.066	0.70
Internalizing	17.79	7.03	9.93	4.71	31.0	−3.08	0.001**	1.31
Externalizing	10.07	3.91	8.00	5.55	61.5	−1.68	0.095	0.43
Total problems	47.93	17.94	30.57	13.25	41.0	−2.62	0.008**	1.10
Activities	6.74	2.98	8.03	2.50	77.0	−0.97	0.345	−0.47
Social	6.86	1.57	7.56	1.92	72.5	−1.18	0.248	−0.40
School	2.94	2.36	2.32	0.45	94.0	−0.19	0.863	0.36
Total Competence	15.93	3.37	17.91	3.94	71.0	−1.24	0.227	−0.54

** $p < 0.01$.

TABLE 4 | Mann–Whitney *U* test comparing continuous variables in the Rorschach Comprehensive System (CS) between children with and without a parent suffering from ALS.

		Study group ($N = 22$)		Control group ($N = 23$)					
CS indexes	**Interpretation (after Exner, 2003)**	***M***	**SD**	***M***	**SD**	***U***	***z***	***p***	**Cohen's *d***
SumV	Self-disgust, shame, emotional distress, guilt	0.73	0.70	0.04	0.21	113.0	−3.92	<0.001***	1.34
FC	Controlled emotional experiences	0.64	0.85	1.96	1.67	126.0	−3.01	0.002**	−0.99
An	Preoccupations concerning body, health or illness	1.16	0.25	0.66	0.14	183.5	−1.79	0.078	2.47
MOR	Negative or blemished features about the self and the world	1.73	1.39	0.65	1.56	104.5	−3.57	<0.001***	0.73
GHR	Positive self-image	1.64	1.62	3.04	1.99	146.5	−2.45	0.013*	−0.77
XA%		64.23	16.52	91.39	9.01	25.0	−5.19	<0.001***	−2.04
X−%	Distorted perceptions	34.00	15.34	7.52	7.43	18.0	−5.35	<0.001***	2.20
Xu%		36.41	14.11	59.00	12.32	57.5	−4.44	<0.001***	−1.71
Sum6		4.64	5.20	1.00	1.31	103.0	−3.49	<0.001***	−0.48
Level 2		0.82	1.30	0.04	0.21	158.5	−2.96	0.003**	0.84
Alog	Thought disturbance	1.32	2.15	0.17	0.65	127.0	−3.42	<0.001***	0.72
CTM		0.86	1.21	0.00	0.00	138.0	−3.59	<0.001***	1.01
WSum6		19.95	23.88	2.74	4.47	88.0	−3.82	<0.001***	1.00
M-		1.27	1.72	0.26	0.45	157.0	−2.48	0.013*	0.80
2AB + (Art + Ay)	Minimizing emotional experiences by intellectualizing	1.59	1.47	0.83	1.07	169.5	−1.99	0.049*	1.39
PTI	Perceptual-thinking index	1.95	1.50	0.09	0.29	57.0	−4.92	<0.001***	1.72
DEPI	Depression index	4.23	1.19	3.57	0.95	169.0	−1.97	0.050	0.61

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 5 | Chi-square comparison of categorical variables in the Rorschach Comprehensive System (CS) between children with and without a parent suffering from ALS.

		Study group ($N = 22$)		Control group ($N = 23$)			
CS indexes	**Interpretation (according to Exner, 2003)**	**Freq.**	**%**	**Freq.**	**%**	**Chi-square**	**p**
SumV > 0	Self-disgust, shame, emotional distress, and guilt	13	59.1	1	4.3	15.72	<0.001***
GHR < PHR	Healthy and adaptive understanding of others	17	77.3	8	34.8	8.22	0.004**
MOR > 1	Negative or blemished features about the self and the world	10	45.5	4	17.4	4.13	0.042*
XA% > 0.90		0	100	16	69.5	23.75	<0.001***
X−% > 0.14	Distorted perceptions	21	95.5	5	21.7	25.05	<0.001***
X−% > 0.25		16	72.7	2	8.7	19.21	<0.001***
M > 0		12	54.5	6	26.1	3.79	0.051
Level 2 > 0	Thought disturbance	9	40.9	1	4.3	8.70	0.003**
Ma < Mp		0	0	4	17.4	4.20	0.040*
PTI > 2	Index of disturbed thinking and distorted perceptions	9	40.9	0	0	11.76	0.001**
DEPI > 4	Higher probability of subclinical or clinical depression	10	45.5	4	17.4	4.13	0.042*
CDI > 3, DEPI > 4	Tendency toward affective problems	3	13.6	0	0	3.76	0.053

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

negative or blemished features about the self and the world (MOR, MOR > 1), more preoccupation with the body, health or illness (An nearing statistical significance, $p = 0.078$), less well controlled or modulated emotional experiences (FC), undesirable self-image (a lower GHR than controls), and less healthy and adaptive understanding of others (GHR < PHR). They had less adequate reality testing results (XA%, XA% > 0.90), more distorted perceptions (X−%) and signs of serious mediational impairments (X−% > 0.14, X−% > 0.25). These children with a parent suffering from ALS also showed more signs

of thought disturbance (Sum6, Level 2, Level 2 > 0, Alog, CTM, WSum6, M−).

The children in the study group revealed other differences vis-à-vis the control children too. They had less unconventional, uncommon, or creative views (Xu%), they more frequently exhibited human movements indicative of general mental abilities, including planning, imagination, and empathy (M > 0). They also tended to minimize emotional experiences by intellectualizing [2AB + (Art + Ay)]. None of the children with a parent suffering from ALS used fantasies as an integral part of their defense system (Ma < Mp).

Among the pathological constellations of the Rorschach CS, the DEPI (i.e., the intensity of depressive affects) was significantly higher in the study group, and significantly more children in the study group (10 of 22, 45.5%) than in the control group (4 of 23, 17.4%) came above the clinical threshold (DEPI > 4) indicating a higher probability of subclinical or clinical depression. Three children in the study group, but none in the control group, had a DEPI > 4 associated with a CDI ≥ 4 (i.e., a positive CDI): this association – which neared statistical significance ($p = 0.053$) – is interpreted as a tendency toward affective problems. Similarly, the index of disturbed thinking and distorted perceptions, Perceptual-Thinking Index (PTI), was significantly higher in the study group than in the control group, and 9 of the 22 children in the study group who completed the Rorschach Test (40.9%) had a PTI ≥ 3, a categorical cutoff that has been found correlated with high thought disorder scores in other tests (Hilsenroth et al., 2007).

The children in the study group did not differ significantly from the controls in the other psychopathological constellations, i.e., the S-CON, the HVI, and the OBS.

Children's Emotional/Behavioral Problems and Competences as Perceived by their Parents

We compared the two groups of children in terms of their emotional and behavioral problems and competences as reported by their healthy parents using the CBCL ($n = 46$ for global scores [Internalizing, Externalizing, and Total Problems]; $n = 40$ for the subscales). The statistical comparisons yielded no significant differences between the two groups for the syndrome and general scales of the CBCL: Anxious/Depressed ($U = 185.0$, $z = -0.41$, *ns*), Withdrawn/Depressed ($U = 155.0$, $z = -1.24$, *ns*), Somatic Complaints ($U = 141.0$, $z = -1.67$, *ns*), Social Problems ($U = 181.5$, $z = -0.51$, *ns*), Thought Problems ($U = 197.5$, $z = -0.07$, *ns*), Attention Problems ($U = 199.5$, $z = -0.01$, *ns*), Rule-Breaking Behavior ($U = 138.0$, $z = -1.75$, *ns*), Aggressive Behavior ($U = 144.0$, $z = -1.54$, *ns*), Internalizing ($U = 196.0$, $z = -1.51$, *ns*), Externalizing ($U = 189.5$, $z = -1.66$, *ns*), and Total Problems ($U = 211.0$, $z = -1.18$, *ns*).

On the other hand, parents of the children in the study group returned significantly lower scores than parents of children in the control group for all competence scales of the CBCL except School ($U = 190.5$, $z = -0.26$, *ns*). More in detail, children with an ALS parent were described as being significantly less competent in: activities ($U = 81.0$, $z = -3.22$, $p = 0.001$), Social ($U = 109.5$, $z = -2.45$, $p = 0.013$), and Total Competence ($U = 88.5$, $z = -3.02$, $p = 0.002$).

Then we applied Pearson's correlation and ICCs to examine the agreement between the scores obtained by the children in the study group and their healthy parents. Moderate to high Pearson's correlations were found for Internalizing, Externalizing, and Total Problems ($r = 0.358$, $r = 0.491$, $r = 0.597$, respectively). The ICCs generated similar results ($\rho = 0.345$, $\rho = 0.462$, $\rho = 0.595$, respectively). Wilcoxon Signed Ranks Tests identified no significant differences between the healthy parents' and their children's assessments of the latter's Internalizing ($z = -0.72$, *ns*), Externalizing ($z = -1.19$, *ns*), and Total problem T scores ($z = -1.64$, *ns*).

Discussion

Our study investigated the emotional and psychological impact of having a parent with ALS on school-age children and adolescents, in terms of adjustment, problem behavior, and personality characteristics, because many studies have explored how patients and caregivers cope with ALS, but none have investigated the psychological impact of the disease on patients' children.

Our findings clearly showed that, compared with a control group of offspring of healthy parents, children who have a parent with ALS experience several emotional and behavioral adverse consequences in terms of global emotional and behavioral problems, internalizing problems, anxiety, and depression, and clinically significant indexes relating to their personality characteristics.

The first aim of our study was to see whether children of a parent with ALS are more at risk of problem behavior than a control group of children with healthy parents. Specifically, children of a parent with ALS reported more emotional and behavioral problems in the YSR, as measured by the Total Problems scale, and more Internalizing problems than the control group. They also had significantly higher scores on two syndrome scales in the internalizing domain of the YSR (Anxious/Depressed and Withdrawn/Depressed), and scores that neared a statistically significant difference on the Aggressive behavior scale of the YSR. Notably, all the corresponding effect sizes were either large (for Anxious/Depressed, Withdrawn/Depressed, and Total Problems) or very large (for Internalizing Problems), indicating that the differences between the scores obtained by the two groups were very clear. A substantial percentage of children with an ALS parent fell within the clinical (42.9%) and borderline (28.6%) ranges for Internalizing problems according to the YSR cutoffs; the difference vis-à-vis the control group was statistically significant.

On the whole, our results are in line with the extant literature suggesting that children can be strongly affected by having a chronically ill parent, especially in terms of internalizing problems (Visser et al., 2005; Sieh et al., 2010) and related symptoms, such as depression, anxiety, and withdrawal (Sieh et al., 2010). ALS in a parent appears to have the same effects on children as any other chronic and/or terminal disease, but the large effect

sizes identified in our sample seem to indicate that children with a parent who has ALS are at substantially greater risk of internalizing behavior than it would seem from the literature on the children of parents with other CMCs. For instance, the meta-analysis conducted by Sieh et al. (2010) yielded a significant overall effect size for self-reported internalizing behavior, indicating that children with a chronically ill parent had more internalizing problems than other children, but the mean effect size was small ($d = 0.25$; 95% CI [0.18, 0.31]). The very large effect size ($d = 1.31$) for self-reported internalizing problem in our sample led us to hypothesize that ALS in parents may have a significantly worse fallout on their children's adaptation than other chronic illnesses. While this issue requires further investigation, two preliminary one-sided outlier tests, carried out to detect whether the effect size for self-reported internalizing problem in our sample is an outlier with respect to the distribution of effect scores reported by Sieh et al. (2010), seemed to confirm this hypothesis (Dixon's Q-test: $p = 0.048$; Grubb's test: $p = 0.017$).

Having a parent with ALS did not increase the scores for somatic complaints in our study group, as reported in other studies concerning CMCs, and MS in particular. Arnaud (1959) found higher levels of body concern in the children of parents with MS, and Pakenham and Bursnall (2006) likewise reported a greater somatization. The latter authors suggested that, in accordance with the social learning model, the children of parents with MS may use somatization to model their parent's illness behavior (Pakenham and Bursnall, 2006). In the light of this interpretation, we speculate that our study children did not express body concern because they were unable to model their parent's illness behavior, possibly because ALS symptoms are too frightening.

Contrary to our expectations, we found no significant differences between our study and control groups in terms of externalizing problems (as reported in many other studies on children with parents suffering from CMCs). To clarify this result, we should consider that the Externalizing score in the YSR consists of two clinical subscales for Rule-Breaking Behavior and Aggressive Behavior. While there were clearly no differences between our two groups of children for the first subscale, on the second the study group revealed higher levels of aggressive behavior than the controls, and the difference neared statistical significance with a medium effect size ($p = 0.066$, $d = 0.70$); increasing the size of the sample would probably make this difference statistically significant. As a possible explanation for this result, there is the interesting suggestion from Sieh et al. (2012) that internalizing problems may buffer against the development of externalizing problems. Children and adolescents with high levels of anxiety, withdrawal, and fearfulness are probably less likely to engage in risk-taking behavior (Sieh et al., 2012).

To sum up, we found that children and adolescents with a parent suffering from ALS had high levels of internalizing problems but few or no externalizing problems. Looking at the broader picture, having a parent with ALS globally affected the children's adjustment – given their significantly higher YSR scores for Total Problems. But analyzing the YSR subscales comprising the Total Problems score showed that the study group's specific reaction pattern was due essentially to internalizing problems and, to a lesser extent, to aggressive behavior. Visser et al. (2005) had likewise reported a prevalence of internalizing problems (withdrawal, somatic complaints, and anxiety/depression) over externalizing problems (rule-breaking or aggressive behavior) in children with parents suffering from cancer.

More in general, our findings are in line with other reports on the profound effect of having a parent with a CMC on a child's functioning, though the combinations of internalizing and externalizing problems may vary. Diareme et al. (2006), for instance, described both internalizing problems (withdrawal, somatic complaints, anxiety/depression) and externalizing problems (rule-breaking and aggressive behavior) in children and adolescents who had a parent with MS. Similarly, Rodrigue and Houck (2001) found an amalgam of internalizing, externalizing, social, identity, and thought problems in a group of children who had parents with various health conditions. In contrast, as Visser et al. (2005) noted, the children of divorced parents reportedly experience more externalizing than internalizing problems (Hetherington and Stanley-Hagan, 1999). We agree that different stressors seem to trigger problems in different areas, and a parent with ALS seems more likely to induce children to turn inward emotionally rather than to exhibit outward-directed behavioral problems (Visser et al., 2005).

The second aim of our study was to test the impact of ALS in parents on their offspring's personality characteristics using the Rorschach CS, in much the same way as Flahault and Sultan (2010) studied adaptation in children with a parent suffering from cancer. Our results reinforce and extend the general picture emerging from the YSR.

First, the Rorschach CS confirmed the substantial impact of ALS in a parent in terms of internalizing behavior and depression in their offspring. The DEPI of the Rorschach CS, which indicates the intensity of depressive affects, was significantly higher in our study group than in the control group, and a significant proportion of the former children (45.5%) scored above the clinical threshold pointing to a higher likelihood of subclinical or clinical depression. It is worth emphasizing that the percentage of children above the clinical threshold for depression in the Rorschach CS (45.5%) was very similar to the percentage of children identified by the YSR as having internalizing problems above the clinical cut-off (42.9%). In other words, the self-report and projective measures converged in indicating that more than 40% of children with a parent suffering from ALS have internalizing-depressive problems.

Second, the structural summary of the children in our study group (obtained with the Rorschach CS) revealed several indicators of difficult adjustment and psychological pain. In their projective responses, these children showed more self-disgust, shame, emotional distress, and guilt. They also experienced more negative or blemished features about the self and the world, an undesirable self-image, less well controlled or modulated emotional experiences, and a less healthy and adaptive understanding of others. The Rorschach CS also generated projective indexes of preoccupations with the body, health and illness that did not emerge from the YSR. A psychodynamic interpretation of this inconsistency might be that these children were worried and

scared about their parent's body, health or illness (as indicated by the Rorschach projections), and they coped with their concern by unconsciously adopting defense mechanisms such as repression, denial, or dismissal. In fact, previous research has shown that physical evidence of a parent's illness and treatment (e.g., a mother's hair loss due to treatment for breast cancer; Forrest, 2006) may have a great impact on children in terms of the distress they experience, and that the impact of a parent's disease is higher, the more their visible symptoms are severe (Kennedy and Lloyd-Williams, 2009).

Overall, the results obtained with the Rorschach CS are particularly congruent with the extant literature on children whose parents have advanced or terminal disease. Kennedy and Lloyd-Williams (2009) investigated how children cope with the distress they experience when a parent is diagnosed with advanced cancer. Children were described as being very distressed by their parent's diagnosis and having concerns relating to their parent's and their own health. Maintaining the appearance of normality and distraction were the prevailing coping strategies used by such children, while having a more limited social activity and greater responsibilities were the most manifest life changes (Kennedy and Lloyd-Williams, 2009).

Another finding emerging from the Rorschach CS in the present study is that our study group had higher scores in several indexes relating to thought problems. The children in the study group proved less adequate in reality testing, they had more distorted perceptions and signs of serious mediational impairment, along with direct evidence of thought disturbance emerging from several scores included in the PTI (Exner, 2000). It is important to bear in mind that the PTI (the result of a thorough revision of the SCZI index) is not meant to be a specific diagnostic indicator of schizophrenia, thought disorder, and psychotic processes (Smith et al., 2001). It should be considered as a tool that can alert clinical psychologists to the possibility of disturbed thinking or cognitive slippage (Smith et al., 2001), conditions that may be interpreted in several ways when found in children with a parent who has ALS.

In our opinion, these indexes should be seen as depending on traumatic events in the children's history, possibly due to the stress associated with a parent's illness. Consistently with this interpretation, Pynoos et al. (1996) reported that Rorschach CS protocols of traumatized adolescents revealed complex psychological profiles, partially similar to those found in our study group. In particular, they highlighted the presence of cognitive problems (revealed through non-normative responses on EA, X+%, Lambda, and F+%), intrusive fantasies and memory disruptions [Schizophrenic index (SCZI) and M−], and loss of self-esteem (Ego Index, MOR, DEPI, and V). In the same vein, Holaday (2000) collected and interpreted Rorschach protocols from children and adolescents diagnosed with posttraumatic stress disorder, finding high scores in the SCZI, DEPI, and CDI indexes, as well as in other variables. The author suggested that, when young victims of traumatic experiences cannot "make sense of what has happened to them, life becomes irrational, illogical, and confusing. Reality is no longer understood in the same way as it was before the trauma [. . .] and the unexplainable, disorganized, and hurtful thoughts and feelings experienced by traumatized children and adolescents are revealed through their Rorschach protocols" (Holaday, 2000, p. 155).

Other studies have identified thought problems connected with post-traumatic experiences in the children of ill parents. Huizinga et al. (2005), for instance, studied the adolescent and young adult offspring of parents diagnosed with cancer, and found that the experience of cancer in a parent may lead to stress response symptoms (i.e., post-traumatic symptoms): in their sample, 21% of the sons and 35% of the daughters of parents diagnosed with cancer had clinically significant stress response symptoms in the form of intrusive thoughts and avoidance behavior, and their stress response symptoms were associated in turn with thought problems and attention problems. Sons and daughters with these clinical stress response symptoms both had significantly higher scores on thought problems and attention problems than adolescents in a norm group (boys also differed from the norm group for anxiety/depression; and girls for withdrawal, somatic complaints, and anxiety/depression). Notably, as the authors highlighted, the incidence of stress response symptoms among children with a parent who had cancer was higher than the incidence seen in other studies among children who experienced cancer themselves. This evidence "suggests that witnessing cancer in a family member may have a more profound impact on a child than being a cancer victim oneself" (Huizinga et al., 2005, p. 293). We hypothesize that witnessing such a devastating terminal illness as ALS in a parent may well produce similar, if not worse effects in terms of the child's stress response and post-traumatic symptoms, with consequent thought problems. However, further research into this aspect is needed.

The third aim of our study was to explore how parents see their children in terms of problem behavior and competences. According to previous literature, it is common for children and adolescents to report experiencing more problems than their parents perceive in them (Stanger and Lewis, 1993; Sourander et al., 1999; Žukauskienė et al., 2004; Watson et al., 2006). Contrary to expectations, the parents and children in our study group showed a moderate to good agreement in reporting problem behavior, and they did not differ in terms of mean internalizing, externalizing, and total problem scores. It was only when compared with the control group that parental perceptions revealed some differences. Parents of the children in the study group awarded significantly lower scores in all competence scales of the CBCL except for School (i.e., Activities, Social, and Total Competence). Specifically, children in the study group were described by their healthy parents as being less capable in a variety of activities (e.g., sports) and social interactions (e.g., friendships) than other children and adolescents of similar age, whereas their school adjustment appeared to be unaffected. In our opinion, these findings indicate that the healthy parent in families with a parent suffering from ALS were aware of their children's difficult life experience and tended not to underestimate their problems. This awareness of the healthy parents and, more in general, the quality of their emotional availability, is a key issue that warrants further investigation in ALS families. Numerous studies concerning other diseases have indicated that the quality of the emotional availability of the healthy parent may compensate for the inattentiveness of the other parent who is ill. For the

children to have a significant relationship with the healthy parent may be fundamental to their psychological adjustment (Davies and Windle, 1997; Leinonen et al., 2003).

In short, our study shows that school-aged children and adolescents who have a parent with ALS are vulnerable and liable to suffer mainly in terms of internalizing behavior and depressive symptoms, and thought problems as a reaction to their stressful condition. Strikingly, about 40% of our sample had scores in the clinical range for internalizing/depressive problems. The healthy parents seemed to confirm this picture and are probably aware of the impact of their spouse's ALS on their children.

Several limitations apply to this study. First, the sample size was not large enough to allow for any reliable generalization of our results. Second, the age range of the children considered was rather wide. The small number of children considered also prevented us from assessing any influence of moderators relating to the children (e.g., age and gender) or the situation (e.g., features of the parent's illness, the patient's neuropsychological and psychopathological profile, parental functioning, and socioeconomic status) that could help to explain the differences in problem behavior between the study group and the controls. A last, potential limitation lies in that we considered more than one child from the same family, thus violating the assumption of statistical independence of our observations. Having said that, we must remember that ALS is a relatively rare disease and it is consequently very difficult to obtain a large number of participants.

Despite its limitations, to the best of our knowledge this exploratory study is the first to address the impact of ALS in a parent on a child's adjustment. We believe that the severe psychological consequences of having a parent with ALS emerging from the present study mean that the families affected may need support to cope with such an overwhelming disease.

Author Contributions

Design and conceptualization of the study: AP, GS, VC. Coding of data: AP, FB. Statistical analysis and interpretation of the data: VC. Drafting the manuscript: VC, FB. Revising the manuscript for intellectual content: VC, FB, EB, MS, MM, CF, GQ, GS, AP. Final approval of the version to be published: VC, FB, EB, MS, MM, CF, GQ, GS, AP. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: VC, FB, EB, MS, MM, CF, GQ, GS, and AP.

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REVIEW
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Patients experiences of maintaining mental well-being and hope within motor neuron disease: a thematic synthesis

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Research is required that can synthesize the experiences of patients with Motor Neuron Disease (MND). One value of being able to do this is to understand the psychological experiences and processes involved in maintaining mental well-being and hope. A qualitative thematic synthesis of studies was undertaken. Studies were electronically searched from inception until June 2014. Twenty-nine studies with 342 (175 male) unique individuals with MND were identified. Five themes were identified: (1)The effects of the disease on interactions, relationships, roles and meaningful activities, (2) Responses that relate to the expression of hope, (3) Factors which disable hope, (4) Factors which enable hope, and (5) Cognitive and Practical adaptation that enabled hope, control and coping. Finally, a model of hope enablement was identified that considers the psychological pathways undertaken by a patient which influence mental well-being and hope. Within this review article evidence is provided which illustrates the central importance of relationships and social support for individuals with MND. Further, it has been identified that periods of coping are possible and are likely associated with greater mental well-being for patients with MND.

Keywords: qualitative, review, motor neuron disease, experiences, hope, adjustment

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Introduction

Motor neuron disease (MND) is a progressive illness which involves the degeneration of lower and upper motor neurons (McLeod and Clarke, 2007). Amyotrophic Lateral Sclerosis (ALS) is the most common form of MND, presenting in over 75% of cases (Lillo and Hodges, 2009), but, for the purposes of this article will be used synonymously with it. Peak onset is between 47–63 years for the familial disease and 47–52 years for the sporadic disease and often has an unpredictable progression thereafter (Kirenan et al., 2011). A general prevalence has been identified in Europe as approximately 2/100,000 (Logroscino et al., 2009) and in the US as 4/100,000 (Mehta et al., 2014). Patients with MND face physical and psychological challenges, including high symptom burden (for instance fatigue, dyspnoea, and pain) as well as the loss of independence and the inability to communicate (Blackhall, 2012).

The psychological aspects of the disease have traditionally been less researched and calls for future research have been suggested to focus on improving and maintaining a patients quality of life (McLeod and Clarke, 2007), of which mental well-being

has an integral role. Mental well-being is defined as a sense of satisfaction, optimism and purpose in life, a sense of mastery, control, belonging, as well as the perception of social support (National Health Service Scotland, 2014). A lack of meaning in life, a central element of mental well-being, has been identified as a predictor of hopelessness for patients with MND (Plahuta et al., 2002; Blackhall, 2012). Hopelessness is one psychological aspect which presents a significant problem for patients with MND (Averill et al., 2007) and is a strong predictor of suicidal ideation (McLeod and Clarke, 2007). The ability to (re)access central aspects of mental well-being may be explained by the recent development of a model of hope enablement (Soundy et al., 2014d), which revolves around the importance of re-establishing an individual's generalized hopes.

Generalized hopes include hopes which exist on different levels, these levels include hope in the following aspects of life; hope for a relief in suffering, hopes which relate to an individual's social roles and responsibilities, hopes which are generated by meaningful and more superficial activities, tasks, accomplishments and interactions (Soundy et al., 2014a,d). It's very likely that the losses experienced by patients with MND exist across the different levels of generalized hopes. For instance, major losses include social interaction, isolation and role changes (McLeod and Clarke, 2007), as well as challenges to independent living (Ozanne et al., 2011). However, positive coping experiences are possible and can be framed around relationships, occupation, employment, leisure activities (Young and McNicoll, 1998). Considering how to initiate, change, improve or restore such losses is essential to maintain a patient's mental well-being. The current model of hope enablement (Soundy et al., 2014a) falls short of considering the processes of adjustment which follow the experience of loss. In particular no consideration is made to the expression of hope, the ability to access adaptive responses or consideration regarding the cognitive processes that an individual may go through following the experience of loss.

The expression of hope (Soundy et al., 2013) in individuals with chronic neurological conditions is directly associated with the adoption of hope or coping strategies which enable access to generalized hopes. Three expressions of hope has been identified in patients with neurological conditions; (1) as a paradox (an expression which illustrates that patients are able to simultaneously accept and defy aspects about their illness and situation), (2) as a dichotomy (considered as either a concrete hope for a cure or complete restoration, or as no hope for improvement, informed by a reaction which included the expression of crisis, loss and disruption), and finally, (3) as transcendence (which represents the patient's embracement of their present situation, as well as being open to a different and altered future). The dichotomy of hope can be seen in patient's expression of hopelessness (an aspect apparent in individuals with MND as identified above) or in their hope for a cure. Hopelessness may be easily experienced for individuals with MND, several reasons may contribute to this, for instance, the disease can be controlling and force passivity, in addition to this individuals can be vulnerable to isolation, frustration, and negative thoughts (Ozanne et al., 2011). Alternatively, hope for a cure can be found in individuals, including hope for a medical cure, from a wish, expectation or a miracle from an individual's faith in God (Fanos et al., 2008). The paradox of chronic illness illustrates the central importance of acceptance for individuals with neurological conditions (Soundy et al., 2013). Indeed, in patients with MND, acceptance is regarded as the most common coping strategy used by patients (Hogg et al., 1994; Montel et al., 2012). Alternatively, examples of transcendence have been identified in patients with MND, for instance, patients with MND are able to positively reframe their situation (Montel et al., 2012). Further to this, evidence that can integrate patients experiences of MND would be extremely useful to the current literature base and could have wider application to other chronic or palliative illnesses. Thus, the purpose of the current review is to consider and synthesize common experiences of MND and better understand the effects of the illness on the patient's mental well-being and generalized hope.

Methods

A thematic synthesis (Thomas and Harden, 2008) was chosen for this review. This method often includes a larger number of studies compared to other qualitative review approaches. One advantage of this is that it helps develop the thematic structure at the level of minor themes or codes (Soundy et al., 2014d). For the purposes of this work we position ourselves as subtle realists (Pope et al., 2007), one reason for this is because we seek to consider the common experiences, perceptions or expressions of individuals. However, we recognize that the synthesis only represents "a truth" and not the truth about the experiences of MND (Weed, 2008).

Search Strategy

The primary author conducted a systematic search of electronic databases from inception until June 2014. The following databases were utilized: CINAHL, AMED, Medline, Embase, PsychINFO, and Sports Discus. The key words utilized included; qualitative OR mixed methods AND experience OR expectation OR Hope AND Motor Neuron Disease Or Amyotrophic Lateral Sclerosis. Further searches included citation chasing of included articles.

Eligibility Criteria

Articles were included when they satisfied the following eligibility criteria, considered within the domains of the "SPIDER" search tool (Cooke et al., 2012).

S—Sample

Studies were included that focused on patients with MND.

PI—Phenomenon of interest

Articles were included when they considered the patient's experience of having MND or other people's (spouse, family, or health care professionals) perception of the patient's experience. Articles were required to focus on and report the domains which related to mental well-being or generalized hopes.

D—Design

Any type of qualitative design was considered including phenomenology, grounded theory, or ethnography. Mixed methods articles were included where a clear qualitative section

was presented. Articles were excluded if they were case studies or reflective pieces; the volume of literature available meant saturation of themes would be achieved without such articles being included. Quantitative research, reviews, books, theses, and conference proceedings were excluded. Internet sources were excluded if not presented in a traditional article form with a methods section which could be critically evaluated.

E—Evaluation

Articles were required to include interviews or focus groups and document experiences, views, or attitudes from users or other people (see above). Where articles reported both patient and carer experiences, articles were only included if data that related to the patient could be separately identified.

R—Result Type

To be included, articles had to contain qualitative results. Articles had to be published in English.

Consolidated Criteria for Reporting Qualitative Studies (COREQ)

The COREQ (Tong et al., 2007) was selected to highlight the quality of reporting in past studies as well as to identify any studies that were considered "fatally flawed." A fatal flaw is defined as a methodological weakness that compromises the trustworthiness of the data (Dixon-Woods et al., 2007). The COREQ contains three domains: The first domain has 8 items which focus on the research team and reflexivity, identifying the positionality of the team, as well as, how and if they are introduced and known to participants. The second domain has 15 items, addressing the methodological orientation of the paper and key processes typically used in methods. The third domain has 9 items which consider the process and procedures of analysis. An adapted form was used following a blind analysis of three random included studies by both authors. A kappa score was calculated (kappa $= 0.43$, $T = 4.3$, $p < 0.001$) and differences in responses compared. Items were adapted where required to clarify scoring (1 point for an item being present, 0 points where it is unclear or absent). The finalized form is available from first author.

Synthesis

Initially open coding was used in an inductive approach to analysis without a-priori concepts intentionally being included. The coding would sometimes use *in vivo* coding to help retain meaning. At the same time, "idea webbing" (Arai et al., 2007; Popay et al., 2007) was used to question how concepts, themes, and sub-themes link together. The sub-themes and codes were then mapped into a framework of themes based on previous findings, relating to the model of hope enablement (Soundy et al., 2014d), generalized hopes (Soundy et al., 2014a) and factors which influence hope (Soundy et al., 2014c). A model was generated using an "idea web" (Arai et al., 2007; Popay et al., 2007) and "concept mapping" (Pope et al., 2007). The model in essence fuses the thematic structure together, making it simplified and focused.

Results

To aid the flow and readability of the synthesis Section Synthesis articles are summarized by numbers[1]

Descriptive

Twenty nine articles (Cobb and Hamera, 1986; Cox, 1992; Young and McNicoll, 1998; Brown, 2003; Murphy, 2004; Hughes et al., 2005; Brott et al., 2006; Hugel et al., 2006; Vitale and Genge, 2006; Brown and Addington-Hall, 2007; Foley et al., 2007, 2014a,b; Fanos et al., 2008; King et al., 2009; Locock et al., 2009, 2012; Locock and Brown, 2010; Gysels and Higginson, 2011; O'Brien et al., 2011, 2012; Ozanne et al., 2011; Hogden et al., 2012; Mckelvey et al., 2012; Whitehead et al., 2012; Gibbons et al., 2013; Mistry and Simpson, 2013; Pavey et al., 2013; Allen-Collinson and Pavey, 2014) were identified following the search. This included a total of 342 patients diagnosed with MND (175 male, 117 female, 50 unknown). Six studies used previously collected data. Mean ages reported 12 studies were between 42 and 68 years and age ranges in studies (reported in $n = 17$ studies) were between 30 and 80 years. The average time since diagnosis (when reported, $n = 6$ studies) ranged between 5 and 40 months. The most frequent location for interview (when reported, $n = 18$ studies) was reported in the participants home. The most frequent geographical location for studies were in the UK ($n = 14$), followed by the USA ($n = 3$), Australia ($n = 2$), and Canada ($n = 2$). Two studies identified cognitive impairment as exclusion criteria (Cox, 1992; Hughes et al., 2005). Two studies explicitly stated that cognitive impairment was not assessed (Murphy, 2004; Brown and Addington-Hall, 2007), although in one study (Brown and Addington-Hall, 2007) patients claimed no cognitive impairment. Other studies identified criteria that may have limited patients who had cognitive impairment. For instance, other criteria included patients who were; willing and able to communicate (Gysels and Higginson, 2011; King et al., 2009), have speech that was understandable (Ozanne et al., 2011), have English language conversational skills (Brott et al., 2006), or be able to "participate" (Allen-Collinson and Pavey, 2014). No additional reference within studies was given to the possible influence of cognitive impairment on results. Supplementary File A contains a figure representing the PRISMA flow diagram and Supplementary File B contains a summary table of included studies.

Between Study Analyses Using COREQ

The average score for the COREQ assessment of studies was 17/32 ($SD \pm 4$). Within domain 1 only one study (1/29) identified what the researcher's occupation was at the time of

[1]Note the following numbers are used to represent articles within Section Synthesis: 1, Allen-Collinson and Pavey, 2014; 2, Brown and Addington-Hall, 2007; 3, Cox, 1992; 4, Fanos et al., 2008; 5, Foley et al., 2007; 6, Foley et al., 2014a; 7, Foley et al., 2014b; 8, Gibbons et al., 2013; 9, Gysels and Higginson, 2011; 10, Hughes et al., 2005; 11, King et al., 2009; 12, Brott et al., 2006; , 13, Brown, 2003; 14, Hogden et al., 2012; 15, Hugel et al., 2006; 16, Cobb and Hamera, 1986; 17, Locock and Brown, 2010; 18, Locock et al., 2009; 19, Locock et al., 2012; 20, Mckelvey et al., 2012; 21, Mistry and Simpson, 2013; 22, Murphy, 2004; 23, O'Brien et al., 2011; 24, O'Brien et al., 2012; , 25, Ozanne et al., 2011; 26, Pavey et al., 2013; 27, Vitale and Genge, 2006; 28, Whitehead et al., 2012; 29, Young and McNicoll, 1998.

the interview or what training and experience the interviewer had received. Only four studies (4/29) identified if a relationship was established prior to conducting the study and only two studies (2/29) identified what the interviewer characteristics were. Within domain 2 considering study design only seven (7/29) used field notes and only six studies (6/29) considered data saturation. Within domain three considering analysis and findings only two studies (2/29) considered details of a coding tree or audit trail and only four studies (4/29) identified minor themes. Ten studies (10/29) scored less than 16 and were discussed for exclusion; however no study was identified as fatally flawed. The complete COREQ assessment table is available from the first author.

Synthesis

Five main themes were identified including; (1) The effects of the disease on interactions, relationships, roles and meaningful activities, (2) Responses that relate to the expression of hope, (3) Factors which disable hope, (4) Factors which enable hope, and (5) Cognitive and Practical adaption that enabled hope, control and coping. In order to obtain the most salient themes (in line with our positionality) codes were reported when at least three studies identified them.

Theme 1: The Effects of the Disease on Interactions, Relationships, Roles, and Meaningful Activities

Individuals expressed specific and significant losses across a range of sub-themes identified below.

Loss and change to personal, social, and occupational relationships

Significant changes for many patients included functional losses that impacted on their vocational, occupational and family roles (1, 7, 9, 11, 16, 18, 20). This could include several roles, for instance, undertaking DIY, being the wage earner for the family, undertaking cooking, or walking children to school. The family role of father, mother, grandparent typically changed by assuming aspects of a patient-carer relationship. An important further change reported was the priority that patients placed on meaningful relationships, typically within the family and spending time with close others (1, 7, 9, 20, 29). Second, the most significant reference to loss included losses to what individuals called "normality" which was detailed as meaningful occupations, voluntary positions, hobbies, travel, pastimes and leisure activities (1, 5, 7, 8, 9, 11, 12, 16, 18, 20, 21, 29). Losses were identified by studies as relating to loss in an individual's social identity or sense of self (7, 11, 13, 16, 17, 18, 19, 25, 26). For instance, one study identified the loss from illness as an "abruption" or a sudden ending of one's previous life or as a "death sentence" (18).

Physical and functional losses and the future implication of loss

The losses to social roles, activities and interactions were related to the reporting of physical and functional loss (1, 2, 3, 7, 8, 9, 10, 11, 12, 16, 17, 18, 20, 26, 28), as well as future worries and what the loss would mean for others (1, 2, 6, 9, 10, 11, 12, 13, 15, 18, 25, 28). Description in articles illustrated the main losses and detail the moments when this was experienced by individuals. The losses include functioning of the legs, arms, communication, breathing, and fatigue, and would often be placed in context by individuals for instance once study identified that: "*Some participants worried about the practicalities of getting to the toilet, or managing drinking or eating, in an unfamiliar environment*" (17). The loss of future contact and relationships were expressed including; not seeing other family members as they grew up without the patient as a support figure, the loss that related to dependency and need for others to undertake even basic tasks for the patient and the ability to cope with such changes.

Theme 2: Responses Relating to the Expression of Hope

Several expressions of hope were identified by patients. The sub-themes group these responses together.

Disorientated response

First, individuals expressed shock, confusion and disbelief at the experiences of symptoms, as well as at diagnosis (2, 13, 14, 15, 17, 19, 20, 21, 23, 26). Symptoms were often and initially identified by individuals as relating to another diagnosis or dismissed for the seriousness of them. However, even when individuals had a better idea of the diagnosis there was still a sense of disbelief and the situation being surreal as well as being devastating. The psychological reactions that appeared to exist over a longer term included the inability to control emotions (11, 15, 16, 18, 23, 25, 26), this included; laughing at feeling helpless, not being able to stop crying, or fluctuating between happiness and sorrow. Patients would also express going between great optimism and despair (2, 18, 26) and ask the question "why me?," not being able to comprehend or have an answer to the question (15, 16, 21, 26).

Responses that disabled hope and coping

Individuals associated the diagnosis with a loss of hope and the hopelessness of living (7, 13, 14, 15, 16, 17, 19, 27). Hope was also affected by increasing loss; however the incurable nature of the disease could create this perception. The hopelessness of their situation extended to the individuals hopes for their life (11, 16, 18, 19, 21, 25) including; the things they had wanted to do or achieve, the hope of possible change, the hope of being able to fight against the illness. Individuals specifically identified a perception of "powerlessness" or the inability to do anything about their situation (2, 11, 13, 14, 15, 19). For some, the disease had ruined the ability to live life (1, 9, 16, 20, 23), indeed patients could identify or report a point in life where they would be better off dead, or at which they would want to die, because at such a stage the suffering was deemed unacceptable (1, 2, 6, 7, 16, 18, 28). This may represent a hope for the suffering to end.

Defiance or challenging the illness

Individuals were able to defy and challenge the illness by positively adapting to it (see Theme 4 and 5). Defiance could be expressed however as a form of denial (2, 3, 5, 14, 15, 17, 21, 23, 26). For instance, patients may not be able to accept the diagnosis

given and this could be related to the sense of shock of having the diagnosis, disbelief that the situation is real, not feeling that anything was wrong, not wanting to know, or not wanting to associate with any others with the illness. Individuals also wanted to defy the illness progression with the aim of curing themselves or being able to survive for longer (2, 5, 11).

Acknowledgement and acceptance

An initial stage of acceptance revolved around patients acknowledging the problem without resigning their life to it or embracing it (2, 5, 6, 7, 9, 12, 13, 18, 19, 23, 25). It represented an awareness of the reality of the disease, but also represented some psychological distance from it. This type of acceptance may have been used as a way to avoid thinking about the implications of the illness, or, not thinking too far into the future. The largest consideration to acceptance could be described as a resignation to acceptance (2, 5, 6, 7, 8, 9, 10, 11, 12, 13, 18, 19, 21, 23, 26, 29), akin to chronic sorrow, this type of acceptance was informed by the uncontrollable nature of the disease and the certain outcome which they faced. This reflected the patient's perception that they were powerless to the outcome and control the disease had in their live.

Embracement or transcendence

Another response closely linked to acceptance that related to resignation but was not identified in such a negative manner was the need to embrace it (2, 6, 9, 10, 11, 13, 15, 16, 18, 19, 20, 21, 23, 25, 29). This expression was associated with focusing on what could be done to aid their situation, including seeing life now as being as good as it can be.

Particularized hopes

Several different forms of particularized hopes were identified including; beating the odds, or that a miracle could occur in reality, or, a wish that 1 day they would wake up and be cured that some abnormality in their condition could assist this (4, 11, 17, 19, 23, 26, 27). A number of patients hoped in a cure from medicine and hoped that advancements in treatments would aid this (2, 4, 16, 21, 26, 27). Finally, some hoped in slowing progression of the illness or for a plateau in progression (16, 19, 25, 27, 28).

Theme 3: Factors which Disable Hope

Patients identified several factors that acted to disable and negatively influence their hopes.

Interactions isolation and relationships

The disease had a significant impact on the actions, interactions and relatedness to others. Patients identified an awareness of meta-perceptions (5, 6, 11, 12, 15, 17, 20, 21, 25). This was typically a negative perception of how others viewed them or an aspect relating to them. Patients appeared more likely to distance themselves from social encounters as a result; there were embarrassment or negative feelings over one's speech and communication style for instance fear of being seen as being "drunk" rather than with an illness, being seen in a wheelchair, or the reliance on others in particular situations. Experiences of stigma were reported and often linked to speech, falling in public and other categories related to the effects of the illness (9, 11, 12, 15, 20, 21, 25). Patients could identify a downwards social comparison/relatedness with peers (4, 14, 16, 17). The reason for this type of comparison was that patients could experience distress at seeing their peers at a more advanced stage of the illness and understanding that this could be them in the future. Others didn't like the content of what was discussed, the nature, or intended purpose of such groups, often preferring to do more "normal" group activities which were not associated with MND. Further to this, some studies identified the negative impact on the patient of watching close others experience their deterioration (13, 15, 18).

Interactions that lacked respect and dignity (1, 11, 12, 13, 14, 19, 23, 25, 26, 28) were perceived by individuals with MND. Such interactions were identified as lacking emotional support and care. For instance, whilst in hospital patients reported feeling that their only use was that of someone that is useful for teaching purposes of medical students. In a similar way, other patients reported interactions that made them feel like a number rather than a person, with medical interactions focusing on the disease presentation. A lack of emotional support and care could leave patients feeling isolated and vulnerable. Several reason for this was attributed to the lack of empathy from staff, staff not giving time to talk about treatment options or advice, a misunderstanding or no understanding of the condition.

A significant lack of satisfaction with interactions and delivery of information was reported by patients (5, 7, 10, 15, 16, 20, 21, 23, 24, 25, 26, 28). One such example was patient's experiences of the referral and interaction process; including uncertainty to the service entitlement, limited time to digest the information or privacy. Other problems highlighted included feeling overwhelmed by information or support once the diagnosis had been given. Finally, individuals identified problems with the continuity of care (13, 14, 15, 19, 20, 24, 28), this included interactions that occurred or was absent between different health care teams and services. Other problems were identified as needing to fight to receive services and there being little consistency in the care team that visited or support individuals.

Problems with informational support

A number of studies identified a general lack of understanding of what MND was (3, 10, 12, 15, 16, 23), most often this was related to health care professionals, but also related to the general public. This could result in patients not wanting to approach health care professionals or not wanting to feel like they had to explain themselves to others who didn't understand. Other problems experienced during interactions with health care professionals included failure to diagnose, giving the wrong diagnosis, or not being willing to disclose diagnosis within the interaction. Further to this, being able to give the patient information relating to prognosis, including practical solutions on how to deal with aspects of the disease, utilizing technology that could assist the individual, advances in treatments and access services. As a result of this, information from health care professionals could be considered as questionable (3, 4, 6, 10, 13, 14, 16, 21, 22, 23, 26, 28).

Loss of control, agency, and autonomy

The process of losing control to the disease as it progresses was significant for patients and was identified as a factor which could only get worse (2, 3, 6, 7, 11, 12, 13, 19, 21). The loss of control could limit the choices of activities individuals participated in and acted to prevented interactions. The uncertainty of the progressive decline and not perceiving what losses were approaching them (pre and post diagnosis), as well as the length of life that is left (post diagnosis) was consistently identified. The fear of death and how a patient would die could be expressed as a severe worry for instance, having difficulties swallowing, or an inability to express oneself when dying. Thus, the effect on, and importance of autonomy was consistently identified as a factor across different stages of the illness which influenced the patient's mental well-being (1, 2, 7, 10, 12, 13, 15, 16, 21).

As the illness progressed, the patients' life became more dependent on others, this meant a life that was more repetitive, limited physically, functionally and socially, and of less interest because of the limitations in autonomy. At later stages of the disease the dependence on others was extremely challenging and impacting on patients (2, 5, 7, 12, 13, 15, 18, 21, 25, 28). The extent of losses in independence meant carers were required to perform basic tasks, making patients feel like a burden and vulnerable. The reason for this was identified as a loss in their privacy and patients would often feel guilty about the stress placed on others. Related to this, patients identified that the disease limited interaction and support through its progressive and intrusive nature, such as not being able to communicate (1, 10, 12, 13, 15, 16, 17, 18, 20, 21, 22, 25, 29). For instance, less individuals who visited the patient, the patient or/and spouse having to give up work, going places or visiting people was made more difficult and could be solely dependent on the support of others, interaction was interrupted, and being part of a conversation was difficult and became less reciprocal in the benefits perceived, or less satisfying and could cease. Further to this, friends could change their interaction with the patient and challenges with spouses could create strain, sadness or even martial break down at the loss of communication.

Finally, individuals experience problems accepting and using functional or technological devices (1, 2, 6, 7, 9, 11, 12, 15, 16, 19, 21, 22). These problems included accepting what the device would mean to them and facing the losses they had experienced or giving up control to the illness, similarly the device could affect an individual self-esteem or image. Further, frustration was caused when the device didn't appear to work effectively.

Experience of negative emotions

Patients could feel and express a range of negative emotions. This included being frustrated (2, 8, 11, 12, 15, 21, 25) at the effects of the illness. This was created by different factors, for instance, taking a long time to get ready, having deteriorated speech, inability to engage in activities once enjoyed and other losses which were important. Patients could also feel sadness and grief about the losses the illness had imposed on their lives (1, 5, 12).

Theme 4: Factors which Enable Hope

Patients identified several factors which were identified as aiding, supporting or enabling hope.

The importance of autonomy, control, and agency

Patients highly valued maximizing the autonomy of their actions and task functions and required that they were respected within interactions (5, 7, 8, 11, 12, 14, 15, 16, 18, 19, 20, 21, 23, 24, 25, 28). Frustration was generated from carers, health care professionals and others undertaking tasks for the patients, assuming they wanted help to undertake the task, or undertake the task at a quicker rate. Also health care professionals that introduced assistive aids e.g., wheelchairs without asking, or medical decisions like having a gastrostomy feed fitted with consulting the patient were deemed as lacking respect and removing autonomy from the patient. The value of autonomy appeared to be that it allowed patients to feel in control, where possible to allow patients to feel a sense of "normalcy" in being independent and stop others imposing and restricting their lifestyle. Losing the capacity to talk was a particular worry which would limit autonomy and control significantly. Related to this, patients consistently highlighted the need for choice and autonomy given during an interaction (5, 6, 7, 9, 12, 14, 15, 20, 24, 25, 26, 28). Within medical care this meant interactions needed to be worded in a way that offered the patient a choice of decision. Bad experiences combined with the need for perceived control could alter the way the patient engaged with services. For instance, patients could exert their control by deciding when to engage with services. Other forms of control may be challenged by others and members of the family telling the patient what they can or can't do before they are ready to lose that role or task, for instance, cooking in the kitchen, getting dressed. Individuals could feel fear and anxiety about their future deterioration, as well as being afraid of death (2, 10, 11, 12, 13, 14, 15, 21, 23, 25, 26, 27, 28). Finally, having control over the end of life decisions was also identified (7, 12, 14, 20, 27, 28). This included euthanasia, decisions about resuscitation or assisted suicide, and circumstances of death like dying at home and having the presence of certain individuals like specialist nurses.

Determination, agency, and useful emotions

Patients identified the need to fight against the illness and not give into it (7, 11, 19). Others identified the need for patient endurance of their situation and having resilience against it, combined with a determination to continue to live (2, 4, 7, 13, 14).

Valued social interactions and support

Patients could relate to peers who were in a similar situation (2, 16, 17, 19, 25, 29). Such individuals could be seen as a role model, and were considered important because they were "similar" others (mostly but not necessarily individuals with MND) who were able to understand their situation. Further to this and more generally, relationships and interaction with others was identified as important (3, 5, 11, 14, 16, 18, 19, 20, 25, 27, 29). This was primarily identified as the care and emotional support received from close others (typically individuals within the family unit), this could include being there for the patient at difficult times

and sharing and valuing them. In some cases for spouses having to care for a patient meant being closer and intimate with them and growing closer together. Examples of this can be seen in two spouses (20); one stated "*Leon still told me that he loved me. He'd write me little love emails*." The other stated "*Kevin would always show me that he loved with his touching*."

The continued expression of strong emotions or feelings, like anger, love through closeness and sexual intimacy was identified as important (1, 7, 13, 16, 20). Emotional support from friends and from health care professionals was identified too, although, not so consistently. The priority of maintaining and using the time left for relationships and interactions with close others was something which became evermore important for individuals (1, 4, 5, 7, 14, 15, 16, 18, 19, 20, 23, 25, 29). The family could enable coping and become a reason to live and continue, or to use medical interventions. In a similar way, peers friends and close others became important to individuals (4, 5, 8, 12, 16, 20, 29). Apart from the benefits of being connected and valued with others, interactions were also beneficial in that they provided a chance for individuals to give back or care for others (5, 16, 17, 18, 19, 27). This allowed individuals to see a sense of purpose from the greater good. Examples of this included making an awareness film about MND, being supportive of others, helping others (like children) accept the patient's death or praying for others.

Patients described the need to retain dignity and feel respected during interactions (5, 7, 12, 13, 15, 23, 25). For instance, having interactions in a private place and seeing that interactions are valued and heard was important. One lady stated "*he (GP) didn't believe me (about symptoms) and he just sort of sent me away and said... 'stop drinking your wine'*" (23). Having health care professionals that were sensitive to the losses were important, for instance, understanding that simple tasks like using a commode can be degrading. A further characteristic valued by patients was the "nature" of other's highlighting the value of individuals who were personable, reassuring and who remained calm (4, 6, 10). Other studies documented the value of humor for patients (4, 11, 16, 18, 20, 29), this included black humor or teasing. For instance, when a friend, who hadn't visited in a while, came around the patient said "*Hello, where the hell have you been?*" (20).

The role and care given by HCPs was identified as important in that support from health care professionals influenced participants mental well-being and coping (4, 5, 12, 14, 16, 23, 26). Health care professionals, including, and notably, professionals from specialized charities were identified as important in providing emotional support as well as decision making. Importantly, patients cited the importance of reassurance and trust from health care professionals (6, 9, 10, 14, 23, 28). Trust was gained by experiencing professionals who were caring and sensitive to the patients' needs. This was particularly important for end of life care (6, 11, 14, 28).

Use and value of tangible support

A number of studies highlighted that patients required physical assistance in increasing quantities (5, 11, 16, 18). This resulted in patients identifying a need for support services and access and utilization of functional or technological aids. A number of patients highlighted the need for different support services which provided tangible assistance to care (3, 11, 14, 16, 17, 21, 25, 26). This included personal care assistance/health care attendance at home, charity services, or care from the hospital. The cost of care could restrict care provision (3, 10, 11, 20). Functional aids were valued by patients (3, 7, 9, 11, 12, 16, 17, 18, 20, 21, 22), this most frequently included systems which aid communication such as an alternative and augmentative communication device. It also included assistive devices that maintained function (e.g., hoists), or devices that enabled continuation of activities (e.g., wheelchairs or mobility scooter), as well as home computers that enabled interaction across the internet.

Theme 5: Cognitive and Practical Adaptation that Enabled Hope, Control, and Coping

Patients identified specific strategies which were used to help them undertake a more self-controlled and dominant response to their losses.

Cognitive adaptation

Several strategies were used by patients in dealing with the symptoms and problems they faced, including: (a) Bringing time closer and focusing on the ability to cope with the present circumstances (2, 10, 14, 18, 25, 27). This meant focusing on coping day by day or week by week, because the presence was more preferable to consider than the future. (b) Dealing with problems as they arrive and affect their life (2, 7, 10, 11, 12, 14, 18, 25, 29). To some extent this limited focus on uncontrollable changes and losses. (c) Focusing on what could be done or achieved (2, 5, 6, 7, 11, 12, 13, 14, 27), rather than what they couldn't or what they had lost. This was seen as enhancing the access of what could be considered "normal." (d) Planning activities and interactions to engage in (4, 8, 11, 12, 14, 20, 27). (e) Using religious faith to aid acceptance, and coping, or hoping for a miracle to occur, or life after death (5, 9, 14, 16, 20, 27, 29). (f) Having the responsibility choice and ownership of how to view the illness and situation. This meant realizing that there was a choice of how to view their situation and that there was a need to make the most of their present circumstances (2, 5, 7, 10, 11, 14, 16, 18, 20, 27, 29).

Pragmatic adaptation

Patients often suggested that the best they could do was to live positively and make the most of the time they had left (2, 10, 11, 14, 15, 18, 20, 27, 29). For instance, doing activities or visiting places that they had wanted to go to but never had. Other individuals wanted a distraction or a break from the illness (7, 10, 11, 14, 17). This was achieved by pretending it is not there, to avoid negative thoughts about what it meant in their life, not reading literature available or associating with MND groups. Other pragmatic adaptation included individuals continuing meaningful activities (4, 5, 7, 9, 10, 12, 14, 15, 16, 17, 18, 19, 20, 25, 27, 29) or continuing being "normal" (1, 2, 5, 7, 9, 17, 18, 24) which provided access to a sense of purpose and meaning as well as valued interactions.

Taking action and searching to enable control

In order to promote a perceived sense of control over the illness taking action and searching provided a sense of purpose and meaning. Individuals consistently identified the need to search for information in order to feel more in control (2, 4, 5, 9, 10, 12, 13, 14, 15, 22, 25, 26), but also take action as a way of controlling aspects of their life that were controllable (2, 4, 5, 11, 12, 14, 18, 19). This included, using alternative therapies (2, 11, 16), adapting health behaviors including rehabilitative exercises, considering care routines, or undertaking hobbies or activities (5, 11, 16) and making dietary adaption (2, 9, 16).

Application of Findings to a Model: Adapting the Model of Hope Enablement (MHE)

The MHE (see **Figures 1**, **2**) is focused on (re)establishing the losses experienced in a patient's life including function, roles, independence, relationships, occupations and hobbies. The model proposes two types of responses to loss which include: (a) a more self-dominant, self-controlled and has the individual as active in that response, alternatively, (b) a more disease/illness dominant and disease controlled response which leaves the individual more passive is possible. The model also identifies factors which influence this. Both responses and the factor which influence hope are detailed above and summarized below.

Factors which may influence the experience of hope

Several factors may influence how loss is experienced and the individual's expression of hope and ability to cope. The above synthesis and list of factors illustrate this. Central factors include the importance of being independent and autonomous for as long as possible, as well as the importance of social support and positive relationships with family and others. This is supported by previous research (Soundy et al., 2014c).

The expression of hope and a more self-initiated and controlled response

This response is made up of several components, exclusively or in conjunction with one another; (a) an acknowledgement, or acceptance of what has happened and understanding of the meaning within their life. Part of this likely requires an acceptance that they are not able to control their situation, as this in itself aids the manageability of the MND (Ozanne et al., 2011). (b) Some form of transcendence (Soundy et al., 2013), for instance, positive cognitive reappraisal or benefit finding of one's situation (Nowlan et al., 2014), or post traumatic growth (Tedeschi and Calhoun, 2004). In essence responses which enables the patient to want to keep living or, an understanding that life may be as good as it can be, or that the experience of the disease provides opportunity for meaning and purpose. (c) The possibility of hope for change, no change, or for less worsening or change of symptoms, useful because it is not a concrete hope and represents a preparedness of the patient to accept what is hoped for may not occur (Soundy et al., 2014b). (d) Some form of a denial related response and/or inability to accept the present circumstances including having a break from the illness, having a future concrete hope of a cure, or rejecting

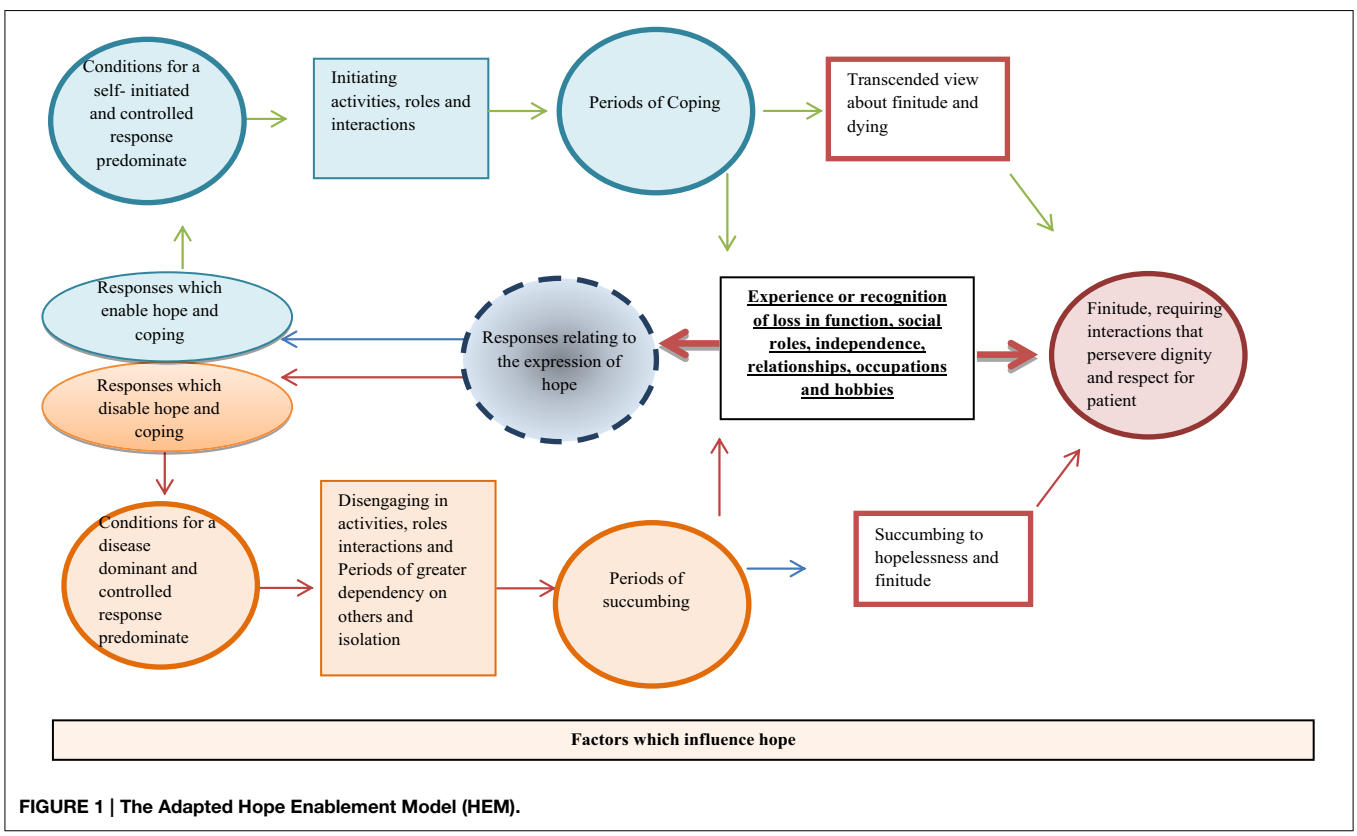

FIGURE 1 | The Adapted Hope Enablement Model (HEM).

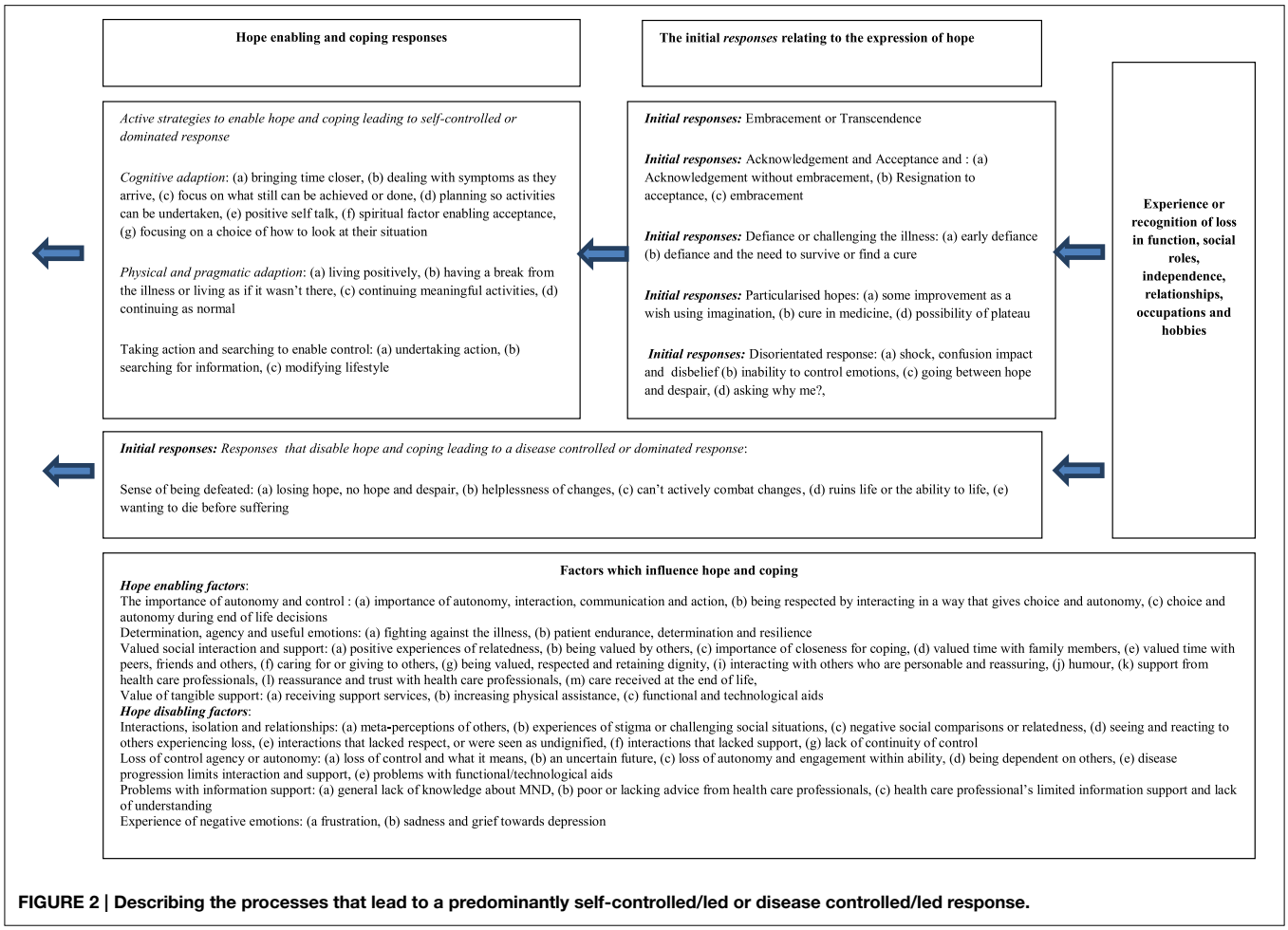

FIGURE 2 | Describing the processes that lead to a predominantly self-controlled/led or disease controlled/led response.

the illness situation. Within patients with MND, denial has been suggested to control the amount of reality that individuals are faced with at any one time; within the current model it clearly provides access to a period of coping. Although, it can be considered problematic if it is continuously used as a strategy (Centers, 2001).

The self-initiated responses are likely to be associated with a degree of agency (Snyder et al., 1991) including want to continue to fight, engage or appreciate living. Further, these responses will also likely be associated with a greater potential for individuals to initiate activities, valued roles and interactions (linked to occupational, voluntary, family, and social) and hence allow factors which enable mental well-being, hope and autonomy to be fostered. Importantly, this response leads to a set of cognitive, pragmatic and action orientated strategies which enable access to engage in meaningful interactions and relationships. In other words, such a response accompanied with specific strategies which allow and promote the following to occur: (1) a sense of meaning and purpose, (2) personal and loving connection, belonging, unity and role fulfillment (family, social, or occupational), (3) a sense of perceived control through more autonomous activity, (4) pleasure, positive feelings and emotions to be generated. For those who have obtained a more transcended view it may be this period of coping extends until nearer death.

The expression of hope and a more disease-dominant and controlled response

The experiences of loss may be perceived as too much, disorientating, overwhelming or past a point of deterioration that is acceptable. The disease controlled response is enforced by the control taken by the illness and the dependency required. Importantly research has recognized the perceived controllability of a stressor as a crucial dimension which influences a patient's coping response (Compas et al., 2012). The disease dominant response is likely informed by the expression of hope and would likely include: (a) A denial of the effects or inability to accept the disease and its meaning because of shock and an inability to comprehend the situation. (b) A consideration of the uncertainty about one's present and future situation and what it means, leading to worry and fear. (c) Resignation to certain future prospects caused by the illness, with a focus on the impossibility of it changing. Thus, what was considered once possibility is now considered impossible. (d) Acknowledging present or future loss beyond the ability or want to live. (e) Being overcome

or disorientated by emotions such as fear and worry when considering the implications of the illness.

These responses are likely associated with, or, have a greater chance of producing disengagement in activities and interactions as well as producing greater periods of dependency on others and isolation. This allows or promotes the following to occur; (1) reduced access to meaningful activities which provide a sense of purpose, (2) a sense that they are in an uncontrollable, unpredictable situation or disease controlled situation, (3) further isolation as connection and unity with others may be challenged. Thus, before another loss is experienced individuals may experience a period of succumbing to the illness, less mental well-being as well as hopelessness about their situation. This may be an aspect which is hard to challenge thus the period of this experience may lead to or continue until a patient's death.

Discussion

The current review has been able to bring together existing information on the experiences of MND, identifying what is known, not known and what further work is needed. Further to this, the research has been able to identify a model of hope enablement combining the expression of hope with cognitive strategies and factors which influence the (re)access of generalized hopes. Importantly, this research identifies that a period of coping is possible for patients and that social support, as well as retaining independence and autonomy are very important for patients with MND.

Interactions, Relationships and Social Support

The current review illustrates that care and loving interactions are especially important from family and close others for maintaining mental well-being. However, the current review supports previous literature which has identified the possibility and danger of a loss of intimacy in relationships as the disease progresses, due to role changes and dependency (Goldstein et al., 1998). Previous literature has identified that social support has a strong association with quality of life (Lulé et al., 2012), is inversely related to a wish to die (McLeod and Clarke, 2007), and has an increasing importance as the disease progresses (Neudert et al., 2001). Thus, there is real value in being able to maintain close and intimate communication with an individual's spouse and family members, because as the disease progresses these relationships, interactions and connections provide a source of hope and comfort for the patient, as well as a sense of meaning in life which likely influences the patient's mental well-being. They are so important because they can last until the patient's death providing a unique source of hope. However, past literature has suggested that patients with a younger age may find greater fluctuations in social support with disease progression (Ray and Street, 2005).

The role and value of peers in the current review highlighted that patients may benefit from groups. Several benefits have been noted by past literature for instance, peers can give advice on how to manage with the disability, or claim benefits or make adaptions to the home. Further to this, being able to help others can provide a sense of satisfaction and being able to relate to others can give a sense of camaraderie, finally seeing others in a worse state but managing could be inspiring (Locock and Brown, 2010). However, being able to access and benefit from the groups could be restricted by several factors including; restrictions imposed by the disease, the location of the group (requiring travel which can't be made), or that patients may not want to identify or socialize with the group. Further, patients may be negatively affected by the loss of peers after a relationship has been established.

Support services can be limited by insufficient homecare, limited access to different members of the multi-disciplinary team, lack of knowledge about MND, diagnostic delays, as well as delivery of the diagnosis (Foley et al., 2012). The consequences of this has been identified in previous literature, for instance late referral to palliative services may negatively impact on the patients quality of life (Bede et al., 2011). In a similar way the lack of awareness of specific care services can have a negative impact on the patient, for instance, within end of life care, health care professionals have identified a lack of awareness of the Preferred Priorities for Care document (Preston et al., 2011). Finally, again in line with the current findings, patients with MND can be dissatisfied with the tangible and informational support provided by health care professionals (Foley et al., 2012). However, strategies to change this have been identified in the current review.

Considerations for Hope

The continued experience of loss and the rapid decline in individuals physical and functional health may explain why individuals can feel hopeless and experience a loss of meaning in life as psychological consequences of MND (Blackhall, 2012). If hope was associated purely with an individual's survival then the experience of hopelessness would be the natural outcome, however, literature considering patients with MND suggests this is not the case. For instance, Centers (2001) describes a hope accessed by patients which is more meaningful than a hope for survival which includes "*a peaceful acceptance of life, and its inexplicable beginnings and endings*" (p. 260), she also notes that hope is tied to the ability to find meaning, this includes connection and loving relationships with others or with God. However, patients in the current review could identify a point where loss was too much or the suffering to great and thus hope for an end to suffering, which has previously been identified as the highest level of hope.

Considerations around Strategies that Enabled Hope

Living with MND often means patients are continually required to adjust to new losses (McLeod and Clarke, 2007). Much of the losses experienced by patients with MND required them frequently interpret and reinterpret the meaning of that loss in their life. Past the expression of hope, individuals broadly identified strategies that were used to enable management of their condition on a daily basis. These strategies may be used to deal with losses which fundamentally challenged their hopefulness, it may be the first or initial stages that promote mental well-being for patients. Much of these strategies could be considered within secondary control or accommodative coping which includes

adapting to stress by reappraisal, acceptance, distraction and positive thinking and, to a lesser extent, passive or disengagement coping which includes ways to avoid stress (Compas et al., 2012). There is evidence of the value of such processes, such as focusing on life in the present moment rather than the future (Centers, 2001). Alternatively, having a break from the reality of their situation may help patients manage their emotions for instance by engaging in activities like playing video games (Roger et al., 2014). Perhaps the most important strategy is positive reappraisal, for instance, in older adults, positive reappraisal can be positively associated with improvements in positive emotions, social relationships, depression and life satisfaction (Nowlan et al., 2014). Further to this, recent literature (Hu et al., 2014) has identified a significant association between mental health (similar to mental well-being defined above) and positive reappraisal. Having a break or avoidance of the illness such as playing video games, listening to music or watching TV has been reported to allow patients to change the meaning of their situation when the reality cannot be changed.

The final set of hope enabling or coping strategies included taking action and searching for meaning and purpose, searching for information and understanding, controlling the controllable aspects of their life, undertaking activities, hobbies or past times, and continuing meaningful activities, some of which could be "normal." To some extent this has been identified previously, for instance, positive effects have been identified in individuals who engage in activities that are social (rather than vocational) such as groups, clubs or classes (McCabe and O'Connor, 2012), although access to work in individuals with brain disorders has also been identified as beneficial (Hartley et al., 2014), the stage and deterioration of patients with MND may not make this accessible. Alternatively, benefit has been found in those who take action by searching for information and gaining understanding (Abdulla et al., 2014). Thus being able to access a more self-initiated response to the illness creates access to meaning and purpose in life and generates mental well-being. It should be noted that many of the strategies identified may have followed some kind of acknowledgement or acceptance from the patient about their situation. Thus, it can be said that acknowledgement and acceptance may lead on and allow patients with MND to more positively approach there situation. This has been found to be an important characteristic in individuals with neurological conditions who are considered to adjust better to their situation (McCabe and O'Connor, 2012).

Considerations to the Model of Hope Enablement

The recent MHE identified by Soundy et al. (2014d) has been substantially updated to include and consider how the expression of hope (Soundy et al., 2013), factors which influence hope (Soundy et al., 2014c) and strategies used by individuals to access generalized hopes (Soundy et al., 2014a) interact and impact on the original model proposed. The current model suggests that periods of coping are possible for patients with MND and that these periods will likely improve a patient's mental well-being. Further, it suggests that these periods are obtained through (re)accessing the sources of generalized hope for individuals. It has also identified the importance for patients of retaining a sense of control over their life situation and circumstances.

Implications for Rehabilitation

Health care professionals and patients alike will be able to consider the model and process that accompany the model. This will aid them to consider how they can engage with patients in a way that allows the patients dignity, respect and promotes autonomy. It is important to note that the current review has not accounted for the impact of cognitive impairment and it is worth noting that a spectrum of cognitive changes will affect patients psychological processes, although only few individuals experience dementia (Achi and Rudnicki, 2012). For instance, the prevalence of frontotemporal dementia has been identified in around 8.1% (CI: 5.6–11.5%) of patients, with apathy, disinhibition and perseveration being the most commonly reported changes (Raaphorst et al., 2012). Thus, where cognitive impairments (Lillo and Hodges, 2009) allow, patients with MND may be able to consider the value of different cognitive strategies from the results and understanding the different way other individuals (re)access there generalized hopes.

Limitations

The analysis and model may have been limited by the first author's knowledge and perception or view of what was contained within the data selected. Unique findings may have been lost because of the type of synthesis used and the positionality taken and the use of a framework to guide the later stages of analysis. That said, the data itself may not reflect the less common experiences of individuals with MND or be able to detail change over time. The critical appraisal of studies identified poor reporting practices, with confidence in individual studies limited by a lack of minor themes and reporting of data saturation. It was not possible to quantify the level of cognitive impairment of the included patients and thus it wasn't possible to determine if and how cognitive impairment would influence individual's hope and mental well-being. It is possible that cognitive impairment could negatively impact on individual's relationships, interactions and meaningful activities and disable hope. Cognitive impairment may also impact individual's cognitive adaptation and emotional expression.

Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fpsyg.2015.00606/abstract

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OPINION
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Communication of diagnosis in amyotrophic lateral sclerosis: stratification of patients for the estimation of the individual needs

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by a progressive loss of the corticospinal tract, brainstem, and spinal neurons, leading to progressive muscle atrophy and weakness, and ultimately to death due to respiratory failure.

The right to be informed is enshrined in the European Oviedo Convention (Council of Europe, 1997). The Awaji diagnostic criteria for ALS are generally used, identifying definite, probable, possible and suspected ALS (de Carvalho et al., 2008). Moreover, the pathway of a correct diagnostic assessment of ALS needs a complex algorithm of knowledge. There are no biochemical markers that allow a definitive diagnosis, and the clinical knowledge of the general practitioner in the early stages is critical in order to direct the patient to the neurologist.

Psychological Assessment

Emotions have not often been studied in ALS. Most existing studies have assessed the psychopathological manifestations involved, essentially depression Ferentinos et al. (2011) and less frequently anxiety. The results have shown that major depressive episodes and anxious episodes are not frequent in ALS patients, although moderate depressive or anxious symptoms are often observed, but less frequently than in other diseases such as multiple sclerosis or Parkinson's disease (Pagnini, 2013).

Patients and their families experience the period of diagnostic assessment for possible ALS with anxiety and distress. When this period is extended, the risk of developing depressive symptoms is greater (Caga et al., 2014). Moreover, a higher prevalence of depression is expected in patients with more severe ALS (Pagnini et al., 2012). In ALS cohorts 7% have minor depression, and 5% have current major depressive disorder (Rabkin et al., 2014). Further, depressive symptoms are significantly related to poorer quality of life (Pizzimenti et al., 2013). A recent study found no correlation between the severity of depression and anxiety and ALS Functional Rating Scale-Revised (ALSFRS-R) score or for disease duration in ALS patients (Chen et al., 2015). However, another investigation of emotional states measured using the Hospital Anxiety and Depression Scale (HADS) showed worsening depression and anxiety scores as ALS progressed (Jones et al., 2014). A recent longitudinal study on "wishing to die" and depression in ALS shows that "wishing to die" is not always expressed in the context of a state of depression and does not necessarily denote psychopathology as such (Rabkin et al., 2014). It is iportant to note that ALS can also be associated not only with psychological problems but also with the impairment of many neuropsychological functions.

Comorbidity with FTD

ALS and FTD could be two ends of the spectrum of one disease (Taes et al., 2010). Approximately 15% of ALS patients show Fronto-Temporal Dementia (FTD) with TDP43 positive inclusions in cortical neurons, whereas at least 50% of them evidence subtle cognitive and/or behavioral dysfunction (Lillo and Hodges, 2009; Lillo et al., 2014). Patients with clinical evidence for both disorders have ALS-FTD. Furthermore, many patients with ALS show some cognitive or behavioral changes without meeting the criteria for FTD; they are described as ALS with cognitive or behavioral impairment (ALS-Ci/Bi). Patients with FTD can similarly show evidence of mild motor neuron involvement without developing ALS: they are said to have FTD-MND.

A significant delay in the time-course of selective attentive processing and a difficulty in initiating and sustaining attention may be present in ALS-b, which points to the possibility of dysfunction in the frontal neural network that responds to novelty and to abnormal integration of associative functions. This attentional impairment should be taken into account when developing alternative communicative strategies in ALS patients (Mannarelli et al., 2014). Although FTD patients exhibit prominent deficits in emotion perception and social cognition, these domains have received relatively little attention in ALS. Performance on emotion processing tasks may provide a useful clinical tool in identifying patients with early FTD-ALS (Savage et al., 2014). Structural and functional neuroimaging have demonstrated that ALS is associated with abnormalities localized mainly in the frontal lobes, and neuropathological investigations have shown the pathological involvement of the prefrontal cortex (Troakes et al., 2012). In FTD structural brain imaging and neuropsychological data involve the functions of the prefrontal cortex. Damage to this region is associated with deficient performance in theory of mind and in affective decision-making, but the relationship between these two capacities in patients with prefrontal cortex dysfunction is unclear. Further neuropsychological or functional studies are indicated as necessary to improve early identification of patients affected by FTD. Comorbidity with FTD should be considered where ALS is diagnosed, and importantly, also when this diagnosis is communicated to patients.

When, What, and How to Communicate Diagnosis

ALS is a deadly disease. The appropriate ways to communicate the diagnosis to patients could be similar to the strategies used in other serious pathologies, such as some variations of cancers with short survival rates.

If ALS is associated with FTD, both diagnoses should be communicated to patients. In this regard the evidence base of good practice in the communication of dementia diagnoses may also be useful for FTD-ALS. For example, in managing newly diagnosed ALS patients, physicians need to consider the following questions: "when, what, and how to communicate the diagnosis?"

When to Communicate the Diagnosis?

The communication of the diagnosis is a complex event: it contains "informative," "prognostic," and "therapeutic" components. The "informative" component or phase provides and defines factual information regarding the medical condition. The "prognostic" component describes the short and long-term implications for the patient and family. The therapeutic component consists of the proposal of a practical plan for management (Karnieli-Miller et al., 2007). In ALS the time of the communication of the diagnosis will often coincide with the communication of prognosis and therapy. The time taken for the informative component is generally shorter than for the other components, which could be reflective of the discomfort of the physician in delivering bad news.

The difficulties for the medical team in making a diagnosis of ALS, and in the moment of communication of the diagnosis to patients has been reported in a recent study (Schellenberg et al., 2014). Physicians and other healthcare workers should learn and implement effective methods for delivering information on the patient's health status (Marcus and Mott, 2014).

The communication process must consider:

- The creation of a strong therapeutic alliance between the entire multidisciplinary team and the patient. A good alliance is critical to subsequent discussion of treatment options (Back et al., 2009). Only within a relationship of reciprocal confidence and trust can the communication of a disease like ALS be understood and processed by the patient. The psychologist is crucial to the creation of this alliance (Marcus and Mott, 2014).
- The comorbidity with FTD and the stage of disease. If the progression of dementia is fast, the communication of diagnosis should be earlier. The diagnosis of FTD and ALS should be communicated when the patient is still able to understand it and to choose his/her own future strategies to cope with his/her illness in accordance with national laws.
- The comorbidity with depression, taking psychological support into account, using measures of risk of suicide. Suicide risk does not exempt the physician from the communication of the diagnosis at a more opportune time.
- The psychological support to the patient and caregiver before and after communication of diagnosis (Miller et al., 2009).

What to Communicate?

The communication about prognosis and evolution in ALS is complicated by the variability of the clinical course and the possible psychopathological and neurological comorbidities. Moreover, patients with ALS-FTD can have increased difficulties with, or lack cognitive resources for, decision-making. In all forms of dementia, despite its importance and implications, the format, content and process of this communication has received insignificant research attention.

The communication should be patient centered and include:

- A clear description of diagnosis, prognosis and therapeutic choices. A truthful but compassionate communication between physicians and patients is essential for decisions

about both disease-directed (curative) and palliative therapies (Rich, 2014).
- Feedback of the patient's understanding about his/her knowledge and acceptance of the disease. This is very important in the case of FTD. The FTD would present impaired anosognosia-related implicit awareness due to a dysfunctional implicit integration of contextual information caused by an abnormal fronto-insular-temporal network (Ibáñez et al., 2013). In FTD, the inhibition, self-monitoring, set-shifting, and mood orientation changes appear to be important skills for awareness of instrumental activities of daily living, while hypo manic mood orientation and a tendency for apathy to be prominent are indications of reduced behavioral awareness (Amanzio et al., 2013).
- The monitoring of the awareness of the patient at the time. Some elderly patients can refuse to receive information about their illness and can abdicate to the paternalistic model of medicine, while other patients tend to search all possible avenues for information. In a survey in Germany 28% of patients and 23% of caregivers used (alternative) resources to find information related to their symptoms before seeing a doctor, mainly from the internet. After the medical visit, although two-thirds were satisfied with the means-disclosure of diagnosis, 88% of patients and 85% of caregivers searched for additional information, most often online and by reading brochures from patients' associations (Abdulla et al., 2014).
- The presence of relatives or caregivers, only if it is accepted by the patient.

How to Communicate the Diagnosis?

Communication of ALS diagnosis may be psychologically traumatic, and patients may need to cope with this by using defense mechanisms as well as individual resources such as resilience. Generally physicians may be unprepared to break bad news, mostly because of a lack of training in emotional management (Pagnini et al., 2012). The relationship between the communication of a negative diagnosis and the response of the patients will depend to a great extent on the manner in which the message is transmitted, but to our knowledge these aspects have been poorly studied in motor neuron diseases.

The method of communicating a diagnosis of ALS should include:

- The application of techniques of counseling, including a comfortable space, adequate time for processing information, respect for the patient and his/her reactions, acceptance of the patient's reactions.
- The possibility of countertransference: the individual health professional should pay particular attention to his or her personal emotions, such as feelings about death.
- Existing evidence based knowledge of methods of communication, for example the Six-Step Protocol for Delivering Bad News used in cancer care (Kaplan, 2010). This includes: setting up the interview, assessing the patient's perception, obtaining the patient's invitation, giving knowledge and information to the patient, addressing the patient's emotions with empathic responses, strategy, and summary.
- The use of simple words that can be understood easily by the patient. The use of euphemisms, vague words, and not naming the disease could be a defense mechanism of the physician (Karnieli-Miller et al., 2007).

In conclusion, communicating a diagnosis of ALS should be done in a way that empowers patients and caregivers in order to improve the disease management and decisions about treatment options. To be effective, it should be individualized, by taking into account several features including:

(a) Stage of the disease at the moment of the diagnosis and possible cognitive impairment;.
(b) Personal characteristics (including personality traits, personal values, possible psychopathological complications like depressive phenomena and mood liability);.
(c) Social and cultural environment of the patient and his/her family, in order to harmonize the communicative process with the values and cultural aspects of the family.

Being part of the medical team and involved from the very beginning in all phases of the healing process, by supporting physicians in their role, the psychologist can prove to be helpful in enhancing it indirectly, as well as directly supporting patients and caregivers.

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Hypnosis-based psychodynamic treatment in ALS: a longitudinal study on patients and their caregivers

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Background: Evidence of psychological treatment efficacy is strongly needed in ALS, particularly regarding long-term effects.

Methods: Fifteen patients participated in a hypnosis treatment and self-hypnosis training protocol after an in-depth psychological and neurological evaluation. Patients' primary caregivers and 15 one-by-one matched control patients were considered in the study. Measurements of anxiety, depression and quality of life (QoL) were collected at the baseline, post-treatment, and after 3 and 6 months from the intervention. Bayesian linear mixed-models were used to evaluate the impact of treatment and defense style on patients' anxiety, depression, QoL, and functional impairment (ALSFRS-r), as well as on caregivers' anxiety and depression.

Results: The statistical analyses revealed an improvement in psychological variables' scores immediately after the treatment. Amelioration in patients' and caregivers' anxiety as well as caregivers' depression, were found to persist at 3 and 6 months follow-ups. The observed massive use of primitive defense mechanisms was found to have a reliable and constant buffer effect on psychopathological symptoms in both patients and caregivers. Notably, treated patients decline in ALSFRS-r score was observed to be slower than that of control group's patients.

Discussion: Our brief psychodynamic hypnosis-based treatment showed efficacy both at psychological and physical levels in patients with ALS, and was indirectly associated to long-lasting benefits in caregivers. The implications of peculiar psychodynamic factors and mind-body techniques are discussed. Future directions should be oriented toward a convergence of our results and further psychological interventions, in order to delineate clinical best practices for ALS.

Keywords: amyotrophic lateral sclerosis (ALS), hypnosis, anxiety, depression, quality of life, defense mechanisms, ALSFRS-r, psychodynamic intervention

Introduction

Amyotrophic Lateral Sclerosis (ALS) erodes patients' personal autonomy and their own freedom in many dimensions of existence. This relentless syndrome mainly affecting the voluntary motor system is characterized by increasing weakness, spasticity, and dysarthric speech. Potential executive dysfunction has been described, susceptibly to demographic variables (Palmieri et al., 2014), in a relevant proportion of cases (Abrahams, 2013). The disease is also featured by secondary symptoms such as pain (Pagnini et al., 2012a), sleep disorders (Blackhall, 2012), emotional lability (Palmieri et al., 2009) and fasciculations (Rana et al., 2009), that generate from mild to severe discomfort in everyday living. In the late stages of the disease, progressing muscular degeneration can evolve in a "locked-in" state in which conscious patients becomes progressively paralyzed and voiceless (Borasio et al., 2001). Death usually occurs due to respiratory failure within 3–4 years from the onset, unless life is protracted by tracheostomy and long term-mechanical ventilation (LTMV). In this case, the patient's life can be extended 10 years or more after the onset in locked-in state (Vianello et al., 2011).

Among the wide range of reactions in which a human being could react to the diagnosis of ALS and its devastating consequences, such as apathy, denial (Ferro et al., 1987) stoicism (Rabkin et al., 2000), resentment, hate, hope (Oster and Pagnini, 2012), or suicidal ideation (Palmieri et al., 2010a), anxiety and depression are probably the most expected features. While their real prevalence is still uncertain (Pagnini, 2013) most studies report values around 30% for anxiety and 40% for depression with some studies reporting values up to 70% for both (Kurt et al., 2007; Wicks et al., 2007; Palmieri et al., 2009; Pagnini, 2013).

Quality of life (QoL) is a further theoretical and clinical issue relevant in ALS that could reasonably be directly associated with physical decline. Several studies suggest, conversely, that ALS patients' QoL is independent of physical impairment (Simmons et al., 2000; Palmieri et al., 2010b; Pagnini, 2013), a phenomenon known as "disability paradox" (Carr and Higginson, 2001), although this relationship is still unclear and motor disability or ALS physical consequences are likely to play a crucial role in determining QoL (Ganzini et al., 1999; Lo Coco et al., 2005). QoL has also been negatively associated to psychological variables such as suffering, sense of burden and hopelessness and positively related mainly to spirituality (McLeod and Clarke, 2007; Pagnini et al., 2011), caregiver relations (Chiò et al., 2004), and mindful attitude (i.e., not evaluating a situation or a context only through previous categorizations, but actively making new distinctions by assuming multiple viewpoints and perspectives; Pagnini et al., 2014a). Fegg et al. (2005) and Roach et al. (2009), highlight a usually undervalued viewpoint, i.e., personality and personal attitudes strongly modulate and shape in a unique manner the possible reactions to ALS.

It is extremely complex to disentangle the specific role of psychological variables, including anxiety, depression, and subjectively perceived QoL from peculiar individual characteristics and physical impairment. It is common clinical experience that these dimensions, in ALS, are very tightly interconnected in a dynamic and reciprocally causative way, forming a circular system not yet thoroughly studied.

Indeed, the great physical burden induced by ALS easily implies negative psychological reactions according to individual traits and attitudes, which, in turn, could weigh on the physical level. This latter aspect has an enormous importance in a disease that substantially lacks medical treatment (Beghi et al., 2011) and reliable physical prognostic factors (Creemers et al., 2014).

The evidence for the strong relation between psychological status and physical outcome in ALS was first provided by a seminal, cross-sectional longitudinal study by McDonald et al. (1994), who found that patients with psychological distress showed a significantly greater risk of mortality than those with higher psychological well-being. Similarly, Johnston et al. (1999) and Krampe et al. (2008) found that mood and personality traits can strongly influence the survival rate of ALS patients. Recently, Pagnini et al. (2014a) showed on a large sample of people with ALS that a mindful attitude attenuates the ALS progression.

It is easy to imagine how being affected by ALS can have devastating psychological impact not only on patients but also on their families, and mostly on their primary caregivers, which are as well at risk of developing depressive and anxiety reactions (Pagnini et al., 2010, 2011; Cipolletta and Amicucci, 2014). It was first reported, in the seminal results by Chiò and his team (Gauthier et al., 2007; Vignola et al., 2008), that whilst in patients depression, anxiety and QoL remained substantially steady, in caregivers there was a significant decrease of Qol and an increase of anxiety and depression along disease progression.

However, notwithstanding the potentially great relevance of the topic, scientific literature quite completely neglected research on the efficacy of psychological interventions. Pagnini et al. (2012c) recently called the scientific community via ALS leading journal to fill this void, highlighting the importance of developing "best practices" for the improvement of QoL and the reduction of psychological distress in ALS patients.

As a first response to this call, Palmieri et al. (2013) published a pilot study on psychodynamic-oriented psychological treatment on ALS, showing the efficacy of a hypnosis intervention together with a self-hypnosis training protocol. The efficacy was proved by measuring pre-post levels of anxiety, depression, QoL, and perceived changes of the aforementioned secondary physical symptoms. Improvements in caregivers' anxiety and depression, probably as a consequence of patients' psychological and perceived physical symptomatology improvement, were also observed. In a further, recent study by Averill et al. (2013), a structural emotional disclosure intervention was proposed to patients with ALS. Authors found their treatment to improve psychological well-being, but argued that their kind of intervention may only be helpful for ALS patients who were unable to express emotions or who had ambivalent attitude about expressing emotion to others. Díaz et al. (2014) demonstrated the benefit, in terms of both anxiety and depression levels, of an integrated intervention based on counseling and cognitive behavioral therapy.

Similarly, Pagnini and colleagues are collecting data from a randomized controlled trial to evaluate the effects of an

ALS-specific meditation training (Pagnini et al., 2014b) on well-being of people with ALS and their caregivers.

Thus, the few and recent research efforts on psychological intervention on ALS displayed very encouraging results, nonetheless they are deeply different in terms of adopted psychological approach, methodology employed and measures used to evaluate the change. Moreover, peculiar individual characteristics that may mediate the change have never been specifically assessed, and no long-term disease progression implications have been studied, so far, in correspondence to specific psychological treatment.

Our aim is to extend our previous (Palmieri et al., 2013) hypnosis-based intervention to a broader ALS group, investigating the longitudinal, long-term effects of intervention on patients and their caregivers, and taking into account the impact on disease progression as well as the influence of individual aspects.

In the direction of this latter goal, we privileged a psychodynamic approach to highlight personality features that could mediate the adaptation to the disease, specifically by focusing on defense mechanisms, which offer an interesting insight into the ego's psychological functioning.

In synthesis, we studied the long-term effects of a brief psychodynamic hypnosis-based intervention on patients with ALS, mainly in terms of their psychopathological and physical symptoms as well as its resonance on caregivers. As a first hypothesis, in line with previous data (Palmieri et al., 2013), we expected positive changes on patients' anxiety, depression, and QoL and that these changes, as measured after the psychodynamic hypnosis-based intervention, would keep stable after 3 and 6 months. Secondly, on the basis of previous results linking psychological well-being and disease progression (McDonald et al., 1994; Johnston et al., 1999; Krampe et al., 2008; Pagnini et al., 2014a), we investigated the possibility of a positive physical effect on disease progression in the treatment group in comparison to the control group. Thirdly, we further hypothesized that these effects of the treatment on patients would also have, as well, an indirect beneficial impact on caregivers' anxiety and depression levels.

Finally, we hypothesized that intrapsychic dynamic factors, such as defense mechanisms, could also represent a starting point in order to take into account both the strictly nomothetic and the idiographic perspectives as complementary (Salvatore and Valsiner, 2010) since the uniqueness of psychological phenomena requires characterizing the dynamics of the individual cases while striving for generalization.

Methods

Participants

Fifteen consecutive volunteering patients with ALS—as members of the treatment group—their respective primary caregivers, and 15 patients with ALS—as control subjects—were recruited via the Motor Neuron Disease Center of the University of Padova Hospital. In synthesis, a total of 45 individuals participated in the study. Participants were informed about the study's purpose and methods and signed informed consent to the study protocol, which was approved by the Ethical Committee of the University of Padova, and carried out in accordance with the principles of the Helsinki Declaration as revised in 1983.

The patients in the treatment group were 7 males and 8 females, with ages ranging from 43 to 73 years ($M = 55.3$, $SD = 8.72$); the mean time since diagnosis ranged between 2 and 37 months ($M = 14.79$; $SD = 11.05$); 11 patients had limbic onset, while 4 had bulbar onset; 4 patients were treated with low dosage antidepressant, 1 patient with anxiolytic, and 11 patients were treated with Rilutek. One of the patients died 6 months after the recruitment, thus only available data was analyzed for this patient. Their caregivers were 12 spouses (5 males, 7 females) and 3 daughters.

The patients in the control group were selected among the available Motor Neuron Disease Centre's longitudinal dataset and were matched for functional disability (ALS-FRS-r; Cedarbaum et al., 1999), age, gender, onset site, time from onset, absence of any cognitive impairment, and were not receiving psychological assistance during the observational time range.

Inclusion criteria for all patients were to have sporadic ALS fulfilling the revised El Escorial criteria for clinically probable or definite ALS (Brooks et al., 2000). Exclusion criteria for patients were the presence of significant neuropsychological dysfunctions or alterations if compared to normative data, while for both patients and caregivers, the presence of concomitant psychiatric or neurological illness, and current use of high-dose psychoactive medications would lead to exclusion. No participant was excluded by these means.

Measures

To assess defense mechanism profile, and thus infer developmental levels in a psychodynamic perspective, we used the Defense Style Questionnaire (DSQ; Bond et al., 1983). The DSQ is a widely used self-report measure of empirically derived groupings of defense mechanism ranked on an adaptive hierarchy. The questionnaire consists of 40 items on a nine point Likert scale, ranging from "Completely Agree" to "Completely Disagree." Four defensive styles labeled maladaptive, image-distorting, self-sacrifice, and adaptive are evaluated. Authors of the Italian validation of the questionnaire (San Martini et al., 2004) suggested mostly using the maladaptive subscale since it has the most items and shows higher reliability.

Trance depth and hypnotizability were assessed through the Hypnoidal State Score (HSS) of the Phenomenology of Consciousness Inventory (PCI; Pekala and Levine, 1982; Pekala, 1991). The PCI is a 53-item self-report inventory that maps 12 major and 14 minor dimensions of subjective experience. In addition to quantifying the experience of being hypnotized, this measure describes various aspects of subjective experience, such as imagery, affects, internal dialog, and alterations in awareness, which were used to tailor subsequent hypnotic interventions according to the patients' features.

The Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) is a broadly used and reliable (Bjelland et al., 2002) self-report measure for caseness and symptom severity of anxiety disorders and depression. It consists of two subscales of 7 items each ranging from 0 to 3: HADS-A, assessing anxiety

and HADS-D for depressive symptoms. Among the wide range of generic depression scales employed in ALS context, the HADS items content seem to be less prone to be distorted by ALS' somatic impairments compared to other common depression measures (Pagnini et al., 2014c). Furthermore, a motor neuron disease's specific version of the HADS has been developed and quantitatively confirmed using Rasch analysis in a study by Gibbons et al. (2011), providing revised scoring and cut-offs that were used for patients in the present study.

The Amyotrophic Lateral Sclerosis Specific Quality of Life—revised (ALSSQOL-r; Felgoise et al., 2009; Pagnini and Simmons, 2010), was used to assess different dimensions of health-related QoL. The ALSSQOL-r is a 46 item disease-specific questionnaire using a 0–10 point Likert scale, with 0 being the least desirable situation, and 10 being the most desirable. It consists of six subscales: Negative Emotion, Interaction with People and the Environment, Intimacy, Religiosity, Physical Symptoms, and Bulbar Function; a Total score, including all the items can be computed and was used in analyses. The ALSSQOL-r was chosen since it provides insights into psychological aspects, spirituality and social issues associated with the disease (Simmons et al., 2006).

Functional impairment owing to ALS was evaluated using the ALS-Functional Rating Scale Revised (ALS-FRS-R; Cedarbaum et al., 1999), which represents the gold standard for neurological evaluation of physical decline imposed by the disease. It consists of 12 items with scores ranging from 0 to 4, with a maximum achievable score of 48 (0 = total disability, 48 = normal) that measures bulbar, upper-extremity, lower-extremity, and respiratory functions.

Procedure and Intervention

Patients underwent complete neurological examination and exhaustive neurocognitive assessment on the same day, about 2 weeks before the psychological treatment, respectively performed by a trained expert neurologist and neuropsychologist with long-term experience with ALS. These evaluations were performed as part of the standardized diagnostic routine at the Motor Neuron Disease Center.

A few days after examination, fully eligible patients of the treatment group underwent a clinical interview performed by a psychotherapist experienced in ALS. This interview was aimed to assess patients' defensive styles (through the DSQ questionnaire) and personality characteristics, crucial in shaping the psychological intervention planning. In this context, patients were encouraged to share possible doubts or curiosity about theoretical premises and expected outcomes, in order to fully inform them about the study and to build clinical alliance. An analogous clinical interview was performed by psychotherapists with caregivers.

The intervention protocol consisted of 4 weekly domiciliary sessions of hypnosis treatment. Each session was conducted by a trained operator in Ericksonian hypnosis accompanied by a further psychologist who administered all the questionnaires and did not remain in the same room during treatment. Each hypnotic session consisted of three phases: the first one was a standardized hypnotic induction based on well-established ideodynamic techniques (Bernheim, 1880) and focused on mind-body relaxation, lasting about 20 min. The second, core phase, lasting from 30 to 45 min, consisted in the administration of therapeutic metaphors, guided visual imagery, and direct and indirect suggestions individually tailored on the basis of the needs of each patient. The conclusive phase of each session consisted of anchoring suggestions aimed to teach self-hypnosis, followed by a slow, guided return to a completely awake state of full consciousness, lasting about 10 min.

While the individual suggestions and metaphors were specifically chosen on a per-patient basis, according to their evolving clinical condition, personality and history, the four sessions were based on fixed themes, common to every patient. In the first session, labeled "safe place," the suggestions and imagery were oriented to a safe and quiet place where the patient could allow his own body and mind to rest and recover in deep relaxation. In the second session, labeled "awareness," the suggestions were focused on developing awareness of individual thoughts, emotions and soothing body's perceptions like the breathing rate. In the third session, labeled "life chain," the suggestions were directed to the change of time focus, and to images of the patients' own familial generations. The fourth and final session, labeled "perceptive," was focused on various imagined perceptions associated to positive emotions and metaphors. After each hypnosis session, perceived trance depth was assessed through the PCI.

The first phase standardized induction, common to all sessions and for all patients, was recorded on an audio compact disk and was left for each patient to listen to in order to enhance self-hypnosis. Patients were encouraged to practice self-hypnosis at least once every day. The whole procedure, including self-hypnosis training, was partially inspired by the protocol by Jensen et al. (2009), Jensen (2011) successfully applied on patients affected by multiple sclerosis in terms of increased well-being.

In synthesis, before the first session and in each follow-up, depression, anxiety levels (by means of HADS) and quality of life (by means of ALSSQOL-r) were assessed. HADS was administered also to caregivers on these occasions. DSQ was assessed only at the preliminary psychological interview, while PCI was administered after each hypnotic session, as it is a specific evaluation of the hypnotic experience.

Information about the presence of the most common ALS secondary symptoms, i.e., pain, sleep disorders, emotional lability, and fasciculations, was verbally collected by the psychologist at the beginning and at the end of treatment.

From an experimental design perspective, outcome variables were anxiety, depression (both for the patients being treated and their caregivers), QoL, and functional disability. These were measured before the intervention (T0), after the last domiciliary session (T1) and on two follow-ups after three (T2), and six (T3) months from the treatment. Since physical functioning alterations, as assessed by ALSFR-r are not appreciable after just 1 month, measurements were collected only at T0, T2, and T3 for both treatment and control patient groups.

Statistical Analysis

Bayesian mixed-models methods were chosen because they offer distinct advantages over classic NHST approaches, such as a more straightforward interpretation of the results (Dienes, 2011), a better handling of outliers and multiple comparisons (Gelman et al., 2012; Aguinis et al., 2013). Furthermore, relevantly to our design, this approach is more robust with small samples and relies on fewer and less strict assumptions on the data (Hoijtink et al., 2008). For a thorough review of the advantages of Bayesian inference in psychological research, see Wagenmakers et al. (2008).

All the analyses were performed with R statistical software, version 3.1.1 (R Core Team, 2014) through the "BayesFactor" package v.0.9.8 (Morey et al., 2014), using non-informative priors. All the Markov Chain Monte Carlo simulations were run with 100,000 iterations.

Regression Analyses

For each of our dependent variables, i.e., HADS-A and HADS-D, ALSFR-r and ALSSQOL-r we performed a Bayesian linear mixed-model regression analysis, considering subjects as a random factor (Id) and observation time-points (labeled "Time"), months since diagnosis, HSS score, DSQ scores, psychopharmacological drugs usage, self-hypnosis practice, and their interactions as fixed factors. We computed a Bayes Factor (BF) of every possible model from our factors, against the simplest model with only the Id random factor. We then chose the most parsimonious model that was not less supported by data than 3 times the one with the highest overall evidence. This cut-off was chosen since smaller BF are described in literature (Jeffreys, 1961) as indicating a "barely worth mentioning," and not "substantial" evidence for the model. The models selected through this statistical approach were also valued in the light of their theoretical soundness against similarly evident models. These two criteria always converged in the choosing of the best models. Finally, we computed the posterior distributions, quantifying uncertainty, for each of the parameters of the chosen models.

Groups Comparison

The comparison between the treatment and control groups were performed through Bayesian hypothesis testing (Rouder et al., 2009; Kruschke and Meredith, 2014). We estimated the difference in means between the two groups ALSFRS-r decline (T3 minus T0 scores) and computed its posterior probability distribution to assess uncertainty. From this distribution, the mean credible value was taken as the best guess of the actual difference and the 95% Highest Density Interval (HDI) as the range where the actual difference is with 95% credibility.

Results

Patients and Caregiver Psychological Measurement

Before treatment (T0), patients had a mean HADS-A score of 7.60 (SD = 3.94), 3 patients' score was in the range for "borderline" cases of anxiety, and 6 patients' score was higher than the "case level" cut-off. After the 6 months follow-up (T3), the mean score was 4.50 (SD = 2.62) and only 1 patient's score was in the range for "borderline" cases of anxiety, and 1 patient's score was higher than the "case level" cut-off.

Before treatment (T0), patients had a mean HADS-D score of 3.27 (SD = 1.98), 5 patients' score was in the range for "borderline" cases for depression, while no patients' score was higher than the "case level" cut-off. After the 6 months follow-up (T3), the mean score was 2.64 (SD = 1.91) and 3 patient's score was in the range for "borderline" cases for depression, and none of the patient's score was higher than the "case level" cut-off.

HADS scores for the treatment group are presented in **Figure 1**. The deceased patient did not have an anxiety or depression score over the cut-offs at any measured time.

ALSSQOL-r scores (**Figure 2**) were in line with the normative data for ALS patients (Felgoise et al., 2009; Pagnini and Simmons,

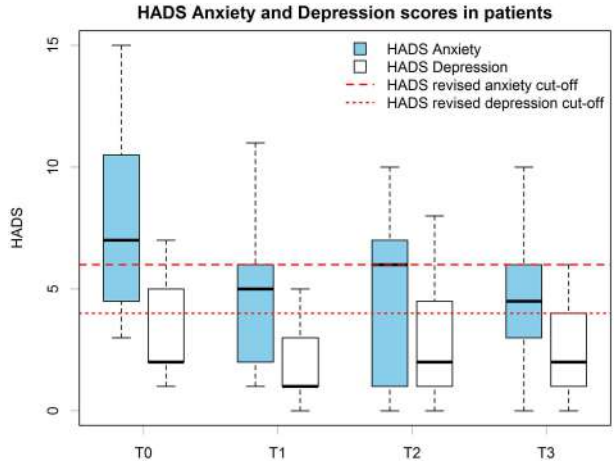

FIGURE 1 | Patients' HADS anxiety and depression scores boxplots at all time points. Scoring and cut-offs are based on the revised version for MND patients.

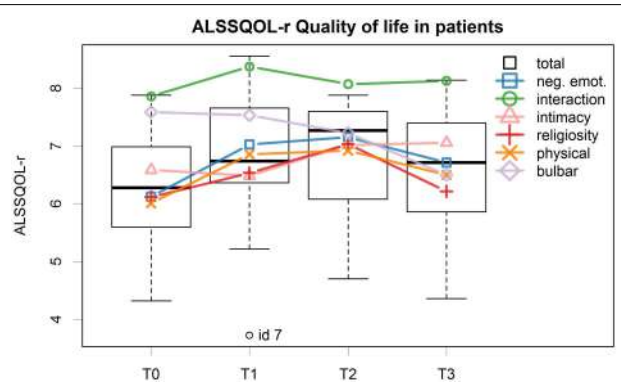

FIGURE 2 | Patients' ALSSQOL-r total scores for all time points are reported in the boxplots, the lines represents the individual subscales.

2010) with a mean total score of 6.83 ($SD = 1.10$) at T0 and of 7.07 ($SD = 1.14$) at T3.

Mean ALSFRS-r score at T0 was 33.13 ($SD = 9.88$) for the treatment group and 31.27 ($SD = 3.90$) for the control group; at T3 these mean scores declined to 31.00 ($SD = 8.13$) for the treatment group and to 23.00 ($SD = 7.25$) for the control group.

The DSQ scores, measured at baseline, showed a very high defensive behavior in treatment group's patients. Specifically the maladaptive ($M = 6.90$, $SD = 1.04$) and image-distorting ($M = 6.73$, $SD = 0.74$) subscales scores, assessing the use of less mature defense mechanisms, were found to be more than the double of the normative data scores for the Italian population (San Martini et al., 2004). Adaptive subscale scores ($M = 3.84$, $SD = 1.36$), in contrast, were comparable to the normative data. The mean scores for patients' and caregivers' individual defense mechanism are reported in **Table 1**.

For each patient, the average HSS score of the four hypnotic sessions was calculated. All the patients were able to successfully achieve an adequate trance depth: 5 out of 15 patients were able to enter a mild hypnoidal state (HSS between 3 and 5), and the remaining 10 patients a moderately hypnoidal state (HSS between 5 and 7).

Before treatment (T0), caregivers had a mean HADS-A score of 9.13 ($SD = 3.72$), 3 caregivers' score was in the range for "borderline" cases of anxiety, and 7 caregivers' score was higher than the "case level" cut-off. After the 6 months follow-up (T3), the mean score was 5.07 ($SD = 3.67$) and only 1 caregivers' score was in the range for "borderline" cases of anxiety, and 2 caregivers score was higher than the "case level" cut-off.

Before treatment (T0), caregivers had a mean HADS-D score of 4.60 ($SD = 3.87$), 1 caregiver's score was in the range for "borderline" cases for depression, while another 1 caregiver's score was higher than the "case level" cut-off. After the 6 months follow-up (T3), the mean score was 2.50 (SD = 3.03) and 2 caregivers' score was in the range for "borderline" cases for depression, and none of the caregivers score was higher than the "case level" cut-off. HADS scores for the caregivers group are presented in **Figure 3**.

TABLE 1 | Individual defense mechanisms' mean scores of patients and caregivers as assessed by Defense Style Questionnaire at baseline.

Defense style	Defense mechanisms	Patients		Caregivers	
		M	*SD*	*M*	*SD*
Maladaptive	Acting out	6.80	1.70	6.19	1.60
	Undoing	6.40	1.84	6.69	1.91
	Passive aggressive	6.69	1.42	6.53	1.35
	Consumption	7.45	2.02	7.24	1.57
	Fantasy	7.29	2.46	4.50	2.69
	Projective identification	8.00	1.81	8.21	2.01
	Help-rejection	6.04	1.94	5.83	1.98
	Projection	7.56	0.91	7.00	1.09
	Regression	7.04	1.75	6.39	2.29
	Withdrawal	5.07	2.85	4.05	2.25
	Somatization	7.71	2.31	7.14	2.33
Image-distorting	Denial	6.17	1.70	6.05	1.29
	Isolation	5.88	1.36	4.66	1.73
	Omnipotence	7.62	1.04	7.23	1.22
	Splitting	7.24	1.52	5.86	1.87
Adaptive	Affiliation	6.40	1.39	5.11	2.56
	Anticipation	3.10	1.84	4.04	2.29
	Primitive idealization	5.32	3.12	5.14	2.70
	Task orientation	3.33	2.78	2.32	1.38
	Pseudo altruism	2.20	1.90	2.50	2.20
	Suppression	3.90	2.23	3.79	1.87
	Sublimation	5.47	3.38	4.14	3.11

Psychological Wellbeing of ALS Patients: Longitudinal Results

Anxiety

The best model selected through the Bayesian linear regression showed a strong effect of the treatment (Time factor) and of the DSQ maladaptive style score but no interaction factors. None of the other considered moderators were present in the most plausible models. **Figure 4**, representing the posterior distributions of HADS-A means at the different time points for the selected model, shows that the reduction in anxiety scores after the treatment kept stable at T2 and T3.

The model showed an overall good fit [BF against "Id only" model = 874, $R^2 = 0.79$, Residual Standard Error (RSE) = 1.92, model parameters are reported in **Table 2**]; additional Bayes Factors are reported in **Figure 5**.

Depression

While the data actually showed a possible reduction in depression after the treatment, patients' depression scores at T2 increased again at pre-treatment levels (**Figure 1**). None of the considered factors in regression analysis showed a relevant linear effect on depression.

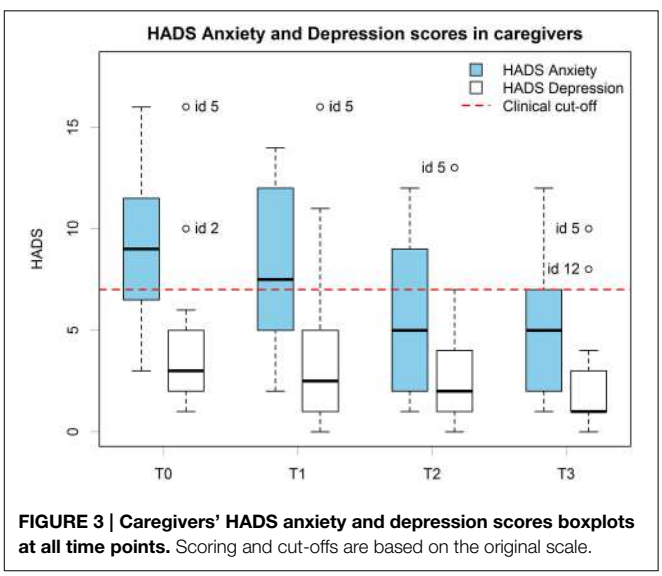

FIGURE 3 | Caregivers' HADS anxiety and depression scores boxplots at all time points. Scoring and cut-offs are based on the original scale.

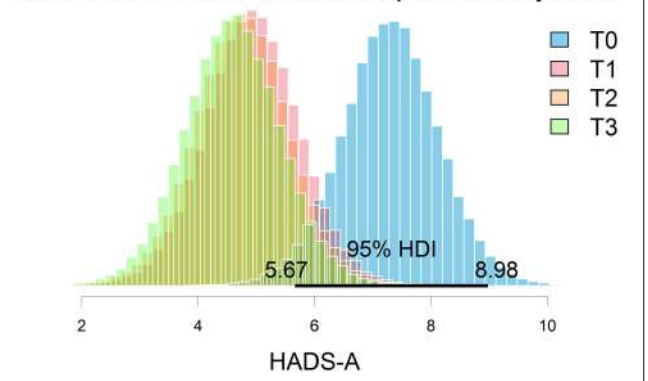

FIGURE 4 | Posterior distributions of anxiety means at the different time points. The 95% HDI represents the area with the most credibility for the exact value. Graphical inspection clearly evidence the decrease in the HADS anxiety score after the treatment, and that this improvement was maintained in the further follow-ups.

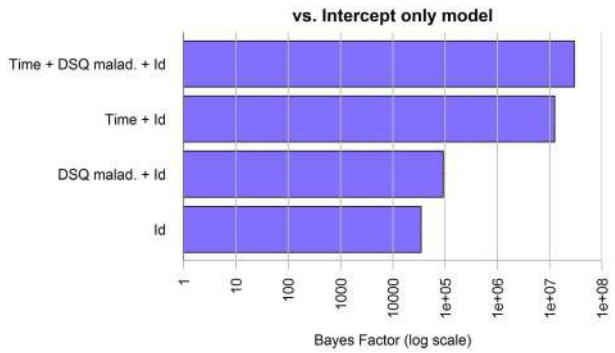

FIGURE 5 | Bayes Factors of the chosen model for anxiety in patients and its simpler nested models against the null model. The bars, on logarithmic scale, represents the ratio of evidence between the different models. Thus, by visual comparison, the weight of each single factor can be inferred.

TABLE 2 | Posterior parameters for HADS-Anxiety best regression model in patients.

Parameter	Mean	*SD*	*SE*
Intercept	5.404	0.717	0.002
T0	1.902	0.450	0.002
T1	−0.460	0.401	0.001
T2	−0.638	0.404	0.001
T3	−0.804	0.418	0.001
DSQ–maladaptive	−1.066	0.686	0.003
$Sigma^2$	3.665	0.846	0.005

TABLE 3 | Posterior parameters for ALS Specific Quality of Life-revised questionnaire best regression model for patients.

Parameter	Mean	*SD*	*SE*
Intercept	6.579	0.269	0.001
T0	−0.232	0.097	<0.001
T1	0.162	0.093	<0.001
T2	0.167	0.093	<0.001
T3	−0.097	0.093	<0.001
$Sigma^2$	0.202	0.047	<0.001

Quality of Life

The best model for the ALSSQOL-R QoL total score showed a relevant, although small, effect of treatment. The score improved at T1 and T2, while at T3 decreased again toward the pre-treatment score. This trend of the Total score was similarly found in most subscales, with the exception of the "bulbar" subscale score, which showed a constant decline, and the "intimacy" subscale score which showed an amelioration only at T2 and kept stable at T3 (**Figure 2**).

The selected model, with QOL predicted by Time and Id, showed an overall good fit (BF against "Id only" model = 8.86, R^2 = 0.82, RSE = 0.45, model parameters are reported in **Table 3**). None of the other considered moderators were present in the most plausible models.

Decline of Physical Functions

For both the patients' groups we computed ALSFRS-r difference scores between pre-treatment and the 6 month's follow up (**Figure 6**). Treatment ($M = -3.98$, $SD = 3.49$) and control group's ($M = -8.64$, $SD = 4.80$) scores were compared through Bayesian estimation. The computed posterior for the difference in groups' means showed a credible average difference of −4.63 with 95% HDI (−8.213, −1.02), which means a 99.3% probability of the real difference value to be smaller than zero (**Figure 7**). The computed Bayes Factor against the "no difference" null model was 6.70, which indicates a substantial evidence in favor of the "difference" model.

Furthermore, we run Bayesian linear mixed-models regression analysis on the treatment group to assess if the decline of the ALSFRS-r score could be predicted by our psychological measures or other factors. The best fitting model, though, showed no effect aside the decline in time (BF against "Id only" model = 7036, $R^2 = 0.95$, RSE = 2.01, model parameters are reported in **Table 4**).

Perceived severity of secondary symptoms, as qualitatively collected in clinical interviews, were compared between pre and post treatment levels: sleep disorders improved in 4 out of 5 patients, pain and cramps improved in 11 out of 14 patients, fasciculations improved in 8 out of 12 patients and emotional lability improved in all of the 7 patients presenting such symptom.

Psychological Wellbeing of Caregivers

Anxiety

The best model selected through the Bayesian linear regression showed an effect of the treatment (Time factor) and the DSQ maladaptive score on caregivers' anxiety, but no interaction

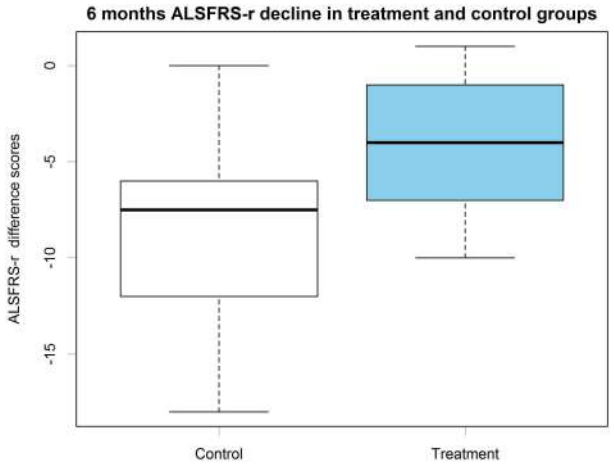

FIGURE 6 | ALSFRS-r 6 months difference scores boxplots in control and treatment groups.

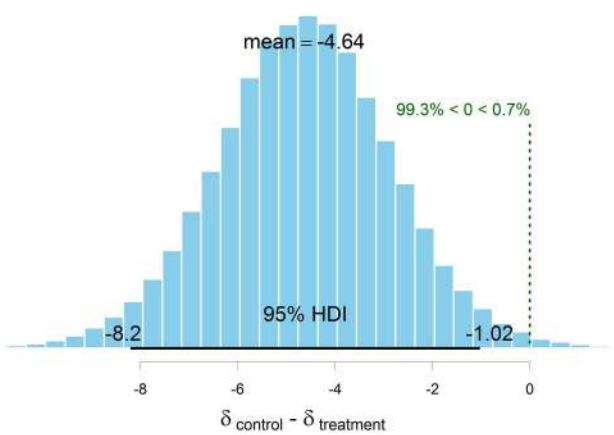

FIGURE 7 | The computed posterior distribution of the true difference in means between experimental and control group decline at 6 months. Since zero lies outside the 95% HDI (the interval that contains the exact value with the most credibility), it can be inferred that the two groups' decline at 6 months is credibly different.

TABLE 4 | Posterior parameters for ALS Functional Rating Scale-revised best model.

Parameter	Mean	*SD*	*SE*
Intercept	31.642	2.697	0.008
T0	1.358	0.441	0.002
T1	1.362	0.441	0.002
T2	−0.481	0.429	0.001
T3	−2.239	0.476	0.002
$Sigma^2$	4.025	0.956	0.005

TABLE 5 | Posterior parameters for HADS-Anxiety best model in caregivers.

Parameter	Mean	*SD*	*SE*
Intercept	6.711	0.831	0.003
T0	2.106	0.449	0.002
T1	0.928	0.428	0.001
T2	−1.381	0.447	0.002
T3	−1.653	0.451	0.002
DSQ–maladaptive	−1.406	0.792	0.004
$Sigma^2$	3.606	0.902	0.005

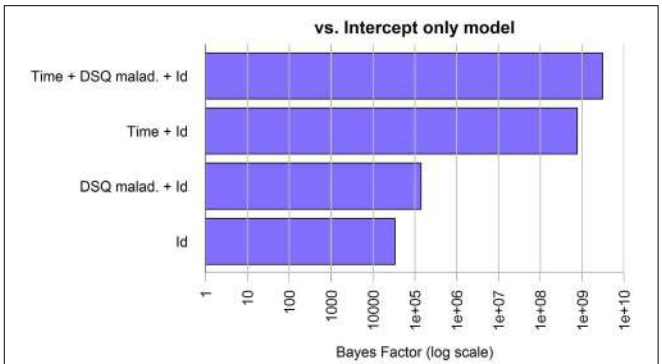

FIGURE 8 | Bayes Factors of the chosen model for anxiety in caregivers and its simpler nested models against the null model. The bars, on logarithmic scale, represents the ratio of evidence between the different models. Thus, by visual comparison, the weight of each single factor can be inferred.

factors. The model shows an overall good fit (BF against "Id only" model > 1000, $R^2 = 0.79$, RSE = 1.90, model parameters are reported in **Table 5**), additional BF are reported in **Figure 8**.

Depression

The best model selected through the Bayesian linear regression showed an effect of the DSQ maladaptive score and of the treatment (Time factor) on caregivers' depression, but no interaction factors. The model shows an overall good fit (BF against "Id only" model > 1000, $R^2 = 0.79$, RSE = 1.90, model parameters are reported in **Table 6**), additional BF are reported in **Figure 9**.

Discussion

The primary goal of the present study was to provide evidence on the efficacy of a hypnosis-based intervention on patients with ALS. Confirming our hypotheses, the results of this longitudinal investigation showed an improvement in wellbeing of patients with ALS, essentially in line with preliminary data observed in our pilot study (Palmieri et al., 2013). Namely, after our hypnotic treatment and autohypnosis training, we observed an improvement in anxiety and depression scores, as measured by HADS (Zigmond and Snaith, 1983). Regression analysis clearly described the improvement in anxiety score, persisting also after

TABLE 6 | Posterior parameters for HADS-Depression best model in caregivers.

Parameter	Mean	*SD*	*SE*
Intercept	3.619	0.711	0.002
T0	0.787	0.362	0.001
T1	0.246	0.330	0.001
T2	−0.411	0.345	0.001
T3	−0.622	0.357	0.001
DSQ–maladaptive	−2.065	0.748	0.004
$Sigma^2$	2.623	0.639	0.004

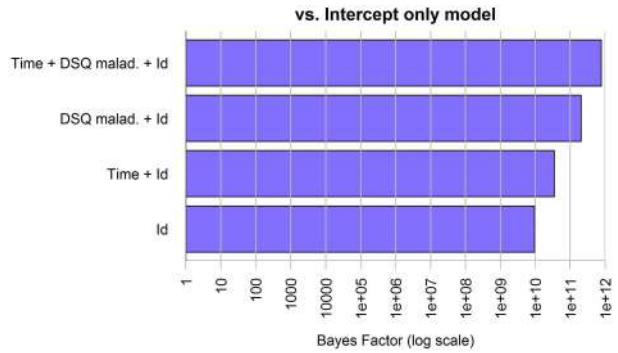

FIGURE 9 | Bayes Factors of the chosen model for depression in caregivers and its simpler nested models against the null model. The bars, on logarithmic scale, represents the ratio of evidence between the different models. Thus, by visual comparison, the weight of each single factor can be inferred.

3 and 6 months, while depression score returned to the pre-treatment level at 3 months not allowing for any of the considered factors to describe satisfyingly its longitudinal trend.

With regard to QoL, as measured by ALSSQOL-r (Felgoise et al., 2009) total score, our best possible regression model described an evident effect of intervention, although of only moderate extent. Specifically we observed an improvement at the end of the treatment and after 3 months, while at the 6-months follow-up the scores turned slightly back toward baseline levels. ALSSQOL-r's individual subscales showed the same trend, except for the "intimacy" subscale, which improved only at 3 months and did not regress at the last follow-up; the "bulbar" subscale, which showed a constant decline; and the "interaction" subscale, which already returned to baseline levels after 3 months.

Bayesian mixed-models regression analysis described no relevant effects of the mild psychopharmacological treatment assumed by five of our patients, nor of their different hypnotizability levels, as assessed by PCI (Pekala, 1991). Analogously, the constancy in the practicing of self-hypnosis after the treatment did not revealed any effect in the study outcomes.

Furthermore, our hypotheses of a link between psychological intervention and physical decline, based on previous studies on ALS describing the psychological status as a moderator for disease progression/survival rate, were confirmed. Specifically we observed an improvement in perceived secondary physical symptomatology immediately after the treatment and, notably, a slower functionality loss, comparing our treated group to a ALS control group, one-by-one matched in terms of age, gender, onset site, time from onset, ALSFRS-r (Cedarbaum et al., 1999) score at baseline and absence of any cognitive impairment. DSQ (Bond et al., 1983) questionnaire was used to assess defense mechanisms profile to individuate the role of intrapsychic factor on psychological status; the DSQ consists of three subscales corresponding to three major defense styles: image distorting, maladaptive, and adaptive, sorted by increasing adaptivity. The scores observed in our patients suggest they strongly rely on the most primitive spectrum of the defense styles. We found some peculiar defense mechanism to be much more represented than others, and overall, patients' scores in maladaptive and image distorting subscale were about the double than those reported in the normative data, while the scores for the adaptive style were comparable to those of the normal population. The treatment had a positive effect on caregivers' anxiety and depression scores as well. This effect was found to persist after 3 and 6 months from the intervention. The DSQ scores regarding the caregivers group substantially mirrored those found for patients with the exception of the "fantasy" defense mechanism, which had a very high score in the patients' group only. Additionally, the maladaptive style score was found to have an effect, constant in time, on anxiety level in patients and on anxiety and depression levels in caregivers. Notably we found no interaction effect between the improvement in time and the DSQ scores either in patients or in caregivers, meaning that the efficacy of the treatment was independent from the amount and type of defenses used.

Each of these aforementioned results, in the context of our main hypotheses, could open a very wide area of discussion, with in-depth theoretical analysis and consequent clinical applications. Among the most relevant results, the firsts that may deserve such a detailed focus are the positive effects of the treatment. Before the intervention, anxiety appeared to be the greater psychological source of suffering in the treatment group's patients, especially in comparison to depression. Specifically, the clear reduction of anxiety scores, immediately after the 1-month hypnotic treatment, was observed to persist during all our data collection period. Consistently with these results, several evidences converge in suggesting that hypnotic state and hypnotizability could be strongly moderated by oxytocin (Bryant et al., 2012; Bryant and Hung, 2013), a hormone implicated, indeed, in social bonding and in the reduction of social anxiety (Radke et al., 2013).

Before treatment, in contrast to anxiety, depression was found at "borderline" levels at most. While the scores decreased after the intervention, the observed depression level was probably too low, at every time point, to appreciate a clearly evident final effect of the treatment.

Although anxiety and depression are frequently described as two strongly related dimensions in ALS literature (Vignola et al., 2008; Atassi et al., 2011; Chen et al., 2015), their different extent measured in our study, could be interpreted in the light of the concerns raised by several authors about

assessment methodologies, in particular for the evaluation of depression levels (Wicks et al., 2007; Gibbons et al., 2011; Gibbons and Young, 2012). Additionally, while undoubtedly linked, anxiety and depression may reveal different complexities regarding their clinical investigation and assessment, given their peculiar nature and pathogenesis. From a psychodynamic perspective, anxiety is typically experienced when a person feels himself to be in impending danger, whether internal (as a consequence of pulsional conflicts) or external (because of real or presumed threats). It is a common clinical experience, other than theoretical assumption, conversely, that depression is a more sophisticate and rich phenomenon, which pervades many life aspects. Furthermore, it is conceivable that the existential despair caused by ALS together with the concomitant challenge to live positively the remaining time, as described by many patients, could generate conflicting feelings poorly represented in the generic items of a standardized questionnaire. The mourning process caused by the progressive and relentless loss of patients' physical functions generates overwhelming experiences of demoralization, hopelessness, anger, and loss of meaningfulness that should not be simply ascribed to "depression" (Blackhall, 2012). Additionally, our current western culture denies and censors the thought of death, even at an institutional level, resulting for instance, in the lack of adequate end-of-life policies, formalized procedures and professionals training observed by Cipolletta and Oprandi (2014) in health care organizations. Such a widespread cultural denial may have relevant psychological consequences, such as the inability to verbally express, or even consciously conceive, the dread caused by the reality of their condition (Testoni et al., 2013). For all of these reasons some aspects of depressive symptomatology may have passed unnoticed.

QoL is as well one of the most important among the yet achievable goals in the context of ALS psychological treatment. In our results, we found that QoL, as a whole, showed a clear immediate positive trend, slightly reverting 6 months after treatment. When compared to the QoL questionnaire sub-dimensions, the intimacy subscale revealed a clear amelioration only 3 months after the treatment, and persisting for the whole observation period. This delayed effect is probably associated with the great improvement in anxiety and depression levels observed in caregivers, which surprisingly kept stable at 6 months after patients' treatment. Such a virtuous circle in which the better psychological wellbeing of the patients positively influences caregivers' one and, vice versa, caregivers' improvement shows a positive impact on patients' psychological status has already been described in some published articles (Chiò et al., 2004, 2005; Lillo et al., 2012; Pagnini et al., 2012b).

Overall, the burden experienced by the caregivers of patients with ALS is often severe and they are at risk of developing depressive and anxiety symptoms (Pagnini et al., 2010). In our opinion, although representing a secondary outcome in our experimental design, the results observed in regard to caregivers may have great relevance also in terms of clinical practice.

As for the verbal content and the administration modality, our hypnosis-based protocol based its theoretical premises on well-established literature on hypnosis, already described as effective in depressive symptomatology (Shih et al., 2009), in anxiety (Saadat et al., 2006; Nash and Barnier, 2012), in the improvement of QoL (Liossi and White, 2001) as well in the treatment of many neurological diseases conditions (Wahbeh et al., 2008). In particular, since suggestions are the core mechanisms withstanding the hypnotic treatment, it can be inferred that those specifically included in our protocol could have promoted the psychological change in patients.

Each of the four selected suggestions themes, while shaped on patients' individual features were conceived to have a role in the conscious and unconscious dynamics, in order to promote long-term benefit. For instance, thinking about the past and the future has been described to lead to increased rumination and well-being loss in ALS patients (Real et al., 2014). By means of hypnosis it is possible to intervene in this painful process, leading to a sense of hopelessness (Plahuta et al., 2002), through the vivid recall of positive imagery of the past and the projection of these symbolic representations into the future, a process which allows to restructure the experience of the self in a coherent and significant temporal dimension. This goal was pursued through the "life-chain" suggestion, based on imageries of generations of ancestors, which were represented behind each patient's own shoulders and the patients' offspring and future generations in front of them. These imageries, while evoking a feeling of hope, triggers patients' support functions, ideas of protection and help, and therefore may reactivate secure attachment figures.

In this vain, many of our hypnotic inspirations included in the suggestions also refer to the attachment theory, in terms of relationships which provide secure-base and safe-haven functions. Clear and stable decrement of patients' anxiety levels, which is one of the main outcome observed in our study, could have partially been due to the symbolic representation of sources of protection conceived in the attachment theory framework, as suggested by Mikulincer et al. (2010).

Another relevant finding of our study is the attenuation of the disease progression, after 6 months, in the treated patients when compared to a well-matched ALS control group. As the number of participants was relatively small, this potentially very relevant finding should be considered cautiously, and requires further investigations to be confirmed. However, this result would be supported by those previous studies showing how a poor psychological state is a significant predictor of subsequent disability and can influence survival rate (McDonald et al., 1994; Johnston et al., 1999; Krampe et al., 2008; Pagnini et al., 2014a). This could be a broader mechanism, not only affecting the person health-related choices, such as advance health care directive for LTMV, as observed by Rabkin et al. (2006).

The association found between the attenuation in disease progression and the concomitant psychological treatment can have several interpretations. It is a fact that the central nervous system changes during hypnosis have been documented by fMRI and EEG studies, and there are many sites in the nervous system in which the overall neural output to skeletal muscle can be modified (Faymonville et al., 2006; Raz et al., 2006). Specifically, hypnosis can have effects on physical parameters such as pain threshold, inflammatory states (for an exhaustive review see

Jensen et al., 2015), and, according to Rossi and colleagues, also at a genomic level (Rossi, 2003).

Indeed, increasing evidence shows that psychophysiological processes, as well as psychotherapy, have an impact on the brain morpho-functional arrangement and genic expression (Benelli et al., 2012; Morath et al., 2014).

However, many questions remain regarding the mechanism that explain the effect of hypnosis in our study. Possibly, the specific muscular relaxation suggestions included in our protocol, could have played a role, independently from the hypnotic phenomenon *per se*, in training patients not to overload, and thus to partially preserve, the still innerved muscular fibers.

While the hypnotic intervention proved efficacious in all treated patients, we did not find any relevant effect of the PCI's HSS index, measuring the individual ability to reach a deeper trance and strongly correlated to classic hypnosis measures, such as the Harvard group scale of hypnotic susceptibility (Pekala and Kumar, 1984, 1987; Forbes and Pekala, 1993), not suitable in a clinical context. Although this result may appear counter-intuitive, in the context of hypnotic research it is not as surprising. The exact relationships between hypnosis components (e.g., hypnotizability, suggestibility, dissociation, relaxation, expectancy, compliance, etc.) are not yet well understood, and high hypnotizability was not found to be necessary, nor predictive for treatment efficacy in other hypnotic intervention contexts as well (Carli et al., 2008).

Finally, particular attention has been devoted to individuate the identification of the defense mechanisms employed by patients, which inevitably modulate the ways the disease is faced, and consequently the psychological reactions. Our data showed an impressive strengthening of the primitive organizational level of defense mechanisms, included in the "maladaptive" and "image-distorting" styles; e.g., projection, regression, projective identification, denial, omnipotence, etc.

A sort of "well-being paradox," meaning that a person shows an apparently good psychological health in the face of an incurable disease, has been observed in terminal patients (Grehl et al., 2011). This phenomenon could be explained by the massive use of denial (i.e., a repudiation of a painfully shared reality and the replacement of it with a more agreeable, individual, version), classically described also in ALS patients (Brown and Mueller, 1970).

Weisman provides an interesting distinction between three aspects of denial in terminal illness (Weisman, 1972). A "first order" denial, in which patients deny the facts relative to his illness; a second-order denial, which prevents the patients from evaluating the extent and the implication of the disease; and a third order denial directed to the image of death itself. In this sense, denial mechanisms could be interpreted more in an "adaptive," rather than "primitive" perspective, in a context that obliges patients to face their own mortality.

Preconceived notions regarding this frequently described defense mechanism in ALS, such as "denial is good" or "denial is bad" do not make sense in the clinical situation. Indeed, denial could serve the patient well if it wards them off anxiety or depression without interfering with treatment compliance or the patient's life goals (Straker, 1998). However, albeit denial was intensively used, the most employed defense mechanism observed in our sample was projection (i.e., attributing to others tendencies originally located and identified within oneself, and then condemned and disavowed), in particular in terms of paranoid thinking. Items related to the idea of other people posing a threat to the patients' own physical and psychical life, received extremely high scores (all patients scored 9 or 10, on a 10 points Likert scale), probably related to that painful feeling of "punishment" wittily detected in clinical interviews with patients by Oster and Pagnini (2012).

Lastly, we observed a strong reliance on the escapist "fantasy" defense mechanism, already observed in patients with ALS by Palmieri et al. (2010a) by means of projective measures. Results of our regression analyses showed that the maladaptive style score was the only factor, aside from treatment, that played a significant role in moderating psychopathological symptoms. Specifically acting as a buffer against the manifestation of anxiety and depression, an effect that was constant in time and active in both patients (although statistically sound only for anxiety) and their caregivers, who showed a very similar pattern of defense mechanisms. These data suggests that the presence of projection and denial, as well as other archaic defense mechanisms, could actually reveal an adaptive reaction to such devastating conditions, and allow to better welcome further treatment as opposed as to what usually happens in clinical psychological practice with patients without physical diseases (McWilliams, 2006).

Among the limitations of the study, the paucity of the sample may restrict the generalizability of the study findings, yet some characteristic of our protocol design represents innovative strength points in respect to the small literature on ALS psychological treatment. Firstly, the patients assessed in the present study were screened for cognitive dysfunctions. This is a relevant issue in the disease (Abrahams, 2013), which is almost never considered in ALS psychological treatment, and is an aspect that may potentially mask the severity and multi-facetedness of psychopathology in these patients. Furthermore, the chosen hypnotic treatment, together with self-hypnosis training, allows for another important goal in the context of such a pervasive disease as other psychological interventions, such as cognitive therapy, require an interactive conversation, which becomes eventually almost impossible as the disease progress toward a locked-in state (Kurt et al., 2007). Self-hypnosis instead is a skill that, once learned, can be reliably used without the need of any muscular activity. In psychodynamic terms, entering a state of self-hypnosis taught in a therapeutic context, allows to reactivate an introjected representation of the therapist as well, together with its associated supporting meanings of a safe relationship.

In synthesis, we highlight the longitudinal, positive effects of our brief psychodynamic treatment, both at psychological level, and most strikingly, at physical level. Our data are similar, for some aspects, to those recently described by Averill et al. (2013); Díaz et al. (2014); Pagnini et al. (2014b), and their teams for treatments, respectively based on expressive disclosure approach, cognitive-behavioral therapy, and mindfulness

meditation training. Still, to the best of our knowledge, this is the first report of a positive long-term effect on disease's progression associated to a psychological intervention in these patients.

On a theoretical level, we tried to approach the complexity of the psychological dynamics in reaction to a devastating disease such ALS, not by searching just for a common personality or typical psychological patterns. We attempted instead to highlight individual peculiarities and integrate them in every design step: in the treatment, in data analysis, by controlling the subject factor, and finally in the results interpretation, moving first steps toward the goal of abductive reasoning (Salvatore and Valsiner, 2010). The abductive generalization (Peirce, 1935), that could represent the key to overcome the opposition between nomothetic and idiographic perspectives, is not only compatible, but arguably strictly interdependent with Bayesian confirmation theory (Douven, 2011) on which the statistical methods employed in our study are based, and we hope that these dialog and perspective could represent the future directions in this research field.

In the clinical practice perspective, patients and caregivers should be aware that hypnotic interventions conjunctly to training in self-hypnosis are relatively easy and inexpensive to provide, and have a plethora of beneficial "side effects." We hope our findings could represents a helpful step in the construction of "best clinical practice," to better manage psychic and physical plagues imposed by ALS disease to patients and their families.

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Psychosocial adjustment to ALS: a longitudinal study

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For the current study the Lazarian stress-coping theory and the appendant model of psychosocial adjustment to chronic illness and disabilities (Pakenham, 1999) has shaped the foundation for identifying determinants of adjustment to ALS. We aimed to investigate the evolution of psychosocial adjustment to ALS and to determine its long-term predictors. A longitudinal study design with four measurement time points was therefore, used to assess patients' quality of life, depression, and stress-coping model related aspects, such as illness characteristics, social support, cognitive appraisals, and coping strategies during a period of 2 years. Regression analyses revealed that 55% of the variance of severity of depressive symptoms and 47% of the variance in quality of life at T2 was accounted for by all the T1 predictor variables taken together. On the level of individual contributions, protective buffering, and appraisal of own coping potential accounted for a significant percentage in the variance in severity of depressive symptoms, whereas problem management coping strategies explained variance in quality of life scores. Illness characteristics at T2 did not explain any variance of both adjustment outcomes. Overall, the pattern of the longitudinal results indicated stable depressive symptoms and quality of life indices reflecting a successful adjustment to the disease across four measurement time points during a period of about two years. Empirical evidence is provided for the predictive value of social support, cognitive appraisals, and coping strategies, but not illness parameters such as severity and duration for adaptation to ALS. The current study contributes to a better conceptualization of adjustment, allowing us to provide evidence-based support beyond medical and physical intervention for people with ALS.

Keywords: ALS, coping, depression, quality of life, longitudinal assessment

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Introduction

Being diagnosed with ALS constitutes for the afflicted person and its social environment a sudden and, considering the whole range of consequences, an unknown, critical life event. Life as known before the illness, with mostly stable social network, clearly defined life conceptions, wishes, plans, and expectations changes drastically. The impact of increasing physical impairment, due to gradual

Abbreviations: ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; QoL, quality of life; BDI, Beck's Depression Inventory; ADI-12, ALS Depression Inventory; SEIQoL-DW, The Schedule for the Evaluation of Individual Quality of Life Direct Weighting; BSSS, Berlin Social Support Scales; MNDCS, Motor Neuron Disease Coping Scale.

loss of motor functions, and the lack of a curative treatment specifically require substantial adaptive strategies from these patients. Against all odds and difficulties most of them report remarkable adjustment outcomes. Over the past two decades, several studies have shown that depression rate in the ALS population is surprisingly low (Kübler et al., 2005; Rabkin et al., 2005; Averill et al., 2007; Hammer et al., 2008; Lulé et al., 2008; Pagnini et al., 2015) and that good quality of life is maintained (Simmons et al., 2000; Goldstein et al., 2002; Nelson et al., 2003; Lulé et al., 2008, 2011). With few exceptions these studies focused on cross-sectional investigations. Most of the longitudinal studies on psychological variables in ALS assessed the various domains of patients' quality of life (Jenkinson et al., 1999; Goldstein et al., 2002, 2006; De Groot et al., 2007; Roach et al., 2009; Montel et al., 2012). All of these seem to agree that quality of life of ALS patients remains relatively constant. Some discrepancies can be observed regarding the relationship between QoL and severity of ALS, most reporting no significant associations (Simmons et al., 2000; Robbins et al., 2001; Goldstein et al., 2002; Lulé et al., 2008; Matuz et al., 2010; Gibbons et al., 2013) or only partially with specific QOL domains (McGuire et al., 1997; Jenkinson et al., 1999; Simmons et al., 2006). The evolution of indicators of mental health, such as depression and anxiety rates has been rarely addressed (Pagnini et al., 2015). The few studies doing so report a relatively high stability of mental health indices (Rabkin et al., 2005; Cupp et al., 2011; Montel et al., 2012; Lulé et al., 2014). However, there is a general problem regarding the assessment of prevalence of depression and anxiety in ALS. Estimation of the prevalence of depressive symptoms has been shown to be difficult (Pagnini, 2013). Determined by the employment of different instruments for the assessment of severity of depressive symptoms, different diagnostic interviews, sample size, and research question, a high variability of percentages reported across studies has been observed (Ferentinos et al., 2011; Pagnini et al., 2015). In an impressive meta-analysis Pagnini and colleagues showed that average scores for depressive symptoms as assessed by questionnaires such as BDI (Beck Depression inventory) or HADS (Hospital Anxiety and Depression Scale) are highly confounded with physical symptoms of the illness which are not necessarily related to depressiveness. They recommend the use of instruments specifically developed for people with ALS, such as the ADI-12 (Hammer et al., 2008) or the use of clinical interview in case of suspicion of a depressive disorder if the communication ability is still preserved (Pagnini et al., 2015).

Due to the fact that ALS patients are permanently challenged in different ways by the progression of their disease it seems reasonable to assess the evolution of their mental health, well-being and psychosocial adjustment indices to optimize support for coping with the disease.

Psychosocial adjustment to chronic illness and disabilities has been defined as a process in which patients have to adjust their internal needs to the new external demands such that they can achieve restoration of the person-environment equilibrium which is disrupted by the new life situation (Livneh and Antonak, 1997). Many factors have been considered when determining the psychosocial adjustment to chronic diseases (Stanton et al., 2007). For example, with respect to HIV and cancer, significant predictive relationships were found between psychosocial adjustment outcomes such as psychological distress and different type of coping strategies and the availability of social support (Stanton and Snider, 1993; Stanton et al., 2007). The model of psychosocial adjustment to chronic disease formulated by Pakenham and colleagues (Pakenham, 1999), being an adaptation of the stress-coping model proposed by Lazarus and Folkman (1984), provides an integrative framework of these factors. According to this, a complex interaction between *illness parameters*, *cognitive appraisal*, *coping resources,* and *coping strategies* determines the psychosocial adjustment to illness. Psychosocial adjustment can be operationalized through affective state and quality of life (Anderson, 2004). In our previous work in a group of 27 patients we applied this model and could identify predictors of psychosocial adjustment to ALS. We showed that social support, appraisal of coping potential and coping strategies such as independence, seeking for support and information and avoidance accounted for most of the variance in QoL, and depression scores (**Figure 1**). The severity of physical impairment and illness duration did not explain any variance in the adjustment outcomes (Matuz et al., 2010).

We continued our model driven research and aimed at assessing the determining variables over time. In the current study we examined weather stress-coping model variables found at T1 would also significantly predict depression and quality of life at T2. Moreover, we assessed the evolution of adjustment outcomes over four measurement time points and explored the changes of model variables over time. We hypothesized that—as for T1—the predicting factors would be cognitive appraisal, coping resources, and coping strategies, but not illness parameters.

Materials and Methods

Materials and Methods have been taken from our previous work (Matuz et al., 2010).

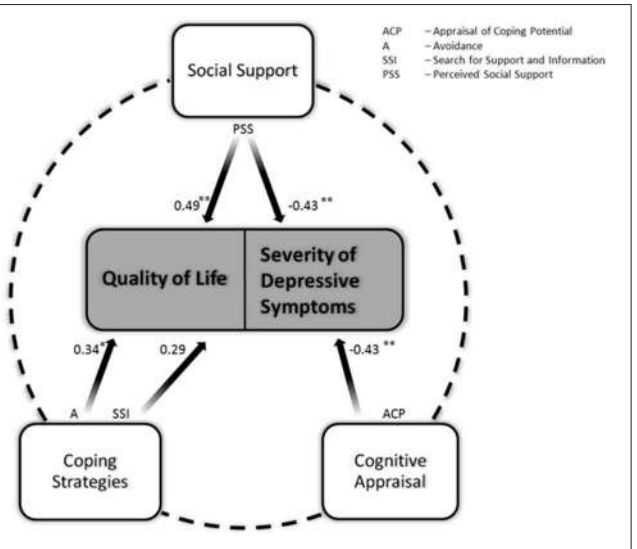

FIGURE 1 | The modified stress-coping model of psychosocial adjustment to ALS on the basis of the cross-sectional regression analyses at T1.

Participants and Procedure

The study was approved by the Ethical Committee of the Medical Faculty, University of Tübingen. The inclusion criterion for patients was a neurologist's diagnosis of ALS according to the El-Escorial criteria. Exclusion criteria were diagnosed frontotemporal dementia, alcoholism and poor knowledge of the German language. We used a longitudinal study design with four assessment time points (T1, T2, T3, and T4). The time between the assessments ranged between 3 and 6 months. Twenty-seven ALS patients (mean age ± *SD*: 55.3 ± 11.1; 35–73; 12 women) participated at T1. Twenty-two, nineteen, and sixteen patients were interviewed at T2, T3, and T4. Reasons for dropout included death (four patients) and deterioration of health (five patients). Two of the patients stated no reason for withdrawing their participation.

Patients were recruited from the ALS outpatient clinic of the Department of Neurology, University of Ulm, from the Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen and through an appeal for participation in the study in a biannual magazine published by the German Society for Muscular Diseases. All patients were visited at their homes by a clinical psychologist (TM), signed informed consent and were interviewed. Patients were interviewed alone, except those ($N = 2$ at T1 and T2, $N = 3$ at T3 and T4) who needed communicative support by caregivers or family members.

Measures

Background Data

Patients' demographic data referred to age, sex, marital status, level of education, and living arrangement and communication abilities, and were obtained with a semi-structured interview.

Illness Parameters

Three illness related variables were assessed: *duration of illness* (month since diagnosis), *dependence on life sustaining treatment* (ventilation and nutrition), and *physical disability* [ALS Function Rating Scale (Cedarbaum et al., 1999) with scores range from 0 = complete paralysis to 40 = normal physical functioning].

Social Support

The Berlin Social Support Scales (BSSS, Schulz and Schwarzer, 2003) was developed based on a multidimensional approach and includes five subscales measuring both cognitive and behavioral aspects of social support: perceived available social support, actually received social support, need for support, search for support, and protective buffering. Patients rated their agreement with the statements from each of the scales on a four-point Likert scale ranging from strongly disagree (1) to somewhat disagree (2), somewhat agree (3), and strongly agree (4). According to the users' manual the scales can be applied in conjunction or separately (Schulz and Schwarzer, 2003). To balance the predictors-sample size ratio we opted for using only the three following scales: perceived, received, and protective buffering.

Coping Strategies

Coping strategies can be classified in four categories: *problem-management, problem-appraisal, emotion-management*, and *emotional-avoidance* (Terry and Hynes, 1998). Problem-management coping strategies describe active attempts to manage the situation (e.g., seek for information) whereas problem-appraisal coping involves attempts to avoid a direct and active confrontation with the problem by either reappraisals of the stressfulness of the situation (e.g., positive thinking) or by behavioral distraction (e.g., positive acting). Emotion-management strategies can be conceptualized as efforts to gain knowledge, to understand, and to express emotions engendered by the situation whereas emotional avoidance represents the active attempts to avoid emotions induced by the stressful events (Terry and Hynes, 1998; Osowiecki and Compas, 1999). Coping strategies were assessed with the Motor Neuron Disease Coping Scale (MNDCS) (Lee et al., 2001). Eighteen items are assigned in six subscales. Patients expressed the extent in which they relied on the coping strategies in the last month using a six-point Likert scale. We integrated the six subscales of this measure in the classification of coping strategies described above, as follows: information seeking and support scales as problem management strategies; positive thinking and positive action scales as problem appraisal strategies; independence scale as emotion management coping and avoidance as emotional avoidance strategy. One score for each type of coping was obtained by generating the mean score of the grouped scales.

Appraisal Components

Patients' primary and secondary appraisals were assessed with four face-valid items designed to measure motivational relevance ("How important are the current events and illness related circumstances in your life?"), motivational congruence ("How congruent is your current life situation with the events and life circumstances you desired to experience?"), problem focused ("How confident are you in your abilities to maintain or change your life situation according to your wishes?"), and emotion focused coping potential ("How confident are you in your abilities to emotionally manage your current life situation?"). The items were originally provided by Smith and Lazarus (1993) and slightly modified to suit the current study population. Patients rated each item on a nine-point Likert scale (one referred to *not at all* and nine to *extremely*). Motivational relevance and congruence are the two components of the primary appraisal and combined appraisals of high relevance and and low congruence define the circumstances as stressful (Smith and Lazarus, 1993). For the analysis we used therefore difference scores of the two primary appraisal components and referred to as appraisal of threat. The two items assessing one's own coping potential (emotion and problem oriented coping) have been concatenated.

Depressive Symptomatology

Severity of depressive symptoms was assessed with the ADI-12 (Hammer et al., 2008), an instrument specifically developed for the assessment of severity of depressive symptoms in ALS. Scores range from 12 to 48. We used a cut-off of $\geq$ 30 to identified patients with severe depressive symptoms, and a more liberal cut-off $\geq$ 23 to identify patients with any depressive disorder including minor depression. The instrument shows excellent internal consistency (Cronbach's $\alpha = 0.91$, Hammer et al., 2008).

Individual Quality of Life

The schedule for the Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW) (Browne et al., 1997) allows the patients to propose five areas of their live which they consider most relevant for their QoL. They then indicate the relative importance of each area and the degree of satisfaction with each of the areas. The resulting SEIQoL index (see Results) ranges from 0 (worst possible QoL) to 100 (best possible QoL). According to a systematic review of 39 relevant studies in which SEIQoL-DW has been employed with a variety of populations, the instrument appears to be a feasible and valid one. Convergent and discriminant validity indices are ranging between moderate and strong (Wettergren et al., 2009).

Statistical Analysis

Normal distribution of the data was tested with Kolmogorov–Smirnov Test. We report the median (*Mdn*) when data were not normally distributed. On continuous data, correlational analyses were conducted to examine whether the dependent and independent variables varied as a function of the background data. Mann–Whitney *U*-test and Kruskal–Wallis *H*-test were applied to categorical data with the same purpose. Non-parametric tests were used with regard to the small sample size and when data were not normally distributed. To compare two variables within the same participants paired samples *t*-test or *Z* Wilcoxon signed-rank test were used. For the comparison of more than two conditions in the same participants, ANOVA or Friedman's ANOVA was computed. To evaluate the relative impact of the significant predictor variables at T1 on the measures of psychosocial adjustment at T2, two regression analyses were conducted separately for depression and QoL scores. This analysis could not be repeated for the rest of time points due to small sample sizes. For depression, the block of predictors included perceived social support, appraisal of coping potential, and emotion management coping (independence scale of the MNDCS). For QoL, we included perceived social support, problem-management coping strategies (information seeking and support), and avoidance. Since no hierarchical assumptions about these predictors were made, all of them were entered in one step using the method Enter. To investigate the relation between the aspects of the predictor variables and adjustment outcome at T2, cross sectional multiple regressions were performed on the dependent variables with the selected subscales of each stress-coping model predictor separately. The subscales on received social support, perceived social support, and protective buffering of BSSS were included in the regression analysis because these subscales are meant for the assessment of social support as a coping resource. The other scales of the instrument were related to coping behavior and, thus, were not included in the regression to avoid overlap with the coping strategy. From the items assessing cognitive appraisals we included primary appraisal of threat and appraisal of coping potential since these are central in the Lazarian stress-coping theory. The independent contribution of the subscales to the prediction of the dependent variable was considered significant only after Bonferroni correction (at $p < 0.01$). Analysis of the model assumptions (i.e., independence of the residuals, absence of outliers, linearity and homoscedasticity) was performed. We used SPSS 15.0 for all statistical analyses.

Results

Most of the patients had spinal onset and sporadic form of ALS. About half of the sample was artificially ventilated (either by mask or through tracheostoma) and approximatively one quarter of the interviewed patients were fed via PEG. The lower/higher education ratio as well as female/male ratio was well-balanced in the current sample. All background and disease related data are listed in **Table 1**.

TABLE 1 | Background information.

	Education*		Sex		Marital status				Artificial ventilation		PEG	
	Lower	Higher	M	F	Married	Single	Widowed	Divorced	Yes	No	Yes	No
T1	48.1	51.9	55.6	44.4	77.8	11.1	7.4	3.7	44.4	55.6	22.2	77.8
T2	45.5	54.5	54.5	45.5	77.3	13.6	9.1	–	40.9	59.1	27.3	72.7
T3	42.1	57.9	63.2	36.8	84.2	15.8	–	–	42.2	57.8	42.1	57.9
T4	37.5	62.5	62.5	37.8	81.3	18.7	–	–	56.3	43.7	37.5	62.5

	Type of ALS		Onset of ALS		Communication****			Living environment	
	Spor.**	Gen.**	B***	S***	Normal	Impaired	Assisted by device	Own household	Nursing home
T1	100	0	7.4	92.6	26	55.5	18.5	92.6	7.4
T2	100	0	4.6	95.4	27.3	31.8	40.9	90.9	9.1
T3	100	0	5.3	94.7	26.3	26.3	47.4	94.7	5.3
T4	100	0	0	100	31.3	25	43.7	93.7	6.3

Lower education refers to 10 years of school (secondary school, first phase) with or without vocational training. Higher education refers to a duration longer than 10 years.

***Spor., Sporadic; Gen., Genetic.*

****B, Bulbar; S, Spinal.*

*****Normal communication refers to normal speech process; impaired communication ranged from "Detectable speech disturbance" to "communication intelligible with repeating"; assisted by devices refers to loss of useful speech and communication exclusively possible by using assistive technology and/or eye movements.*

TABLE 2 | Descriptives for depression and quality of life over the measurement time points.

Assessment time point	T1		T2		T3		T4	
Sample size	***N* = 27**		***N* = 21**	***N* = 22**	***N* = 18**	***N* = 19**	***N* = 15**	***N* = 16**
Outcome	QoL	D	QoL	D	QoL	D	QoL	D
Mean/Mdn	67.79	22.5	66.67	23	67.56	21.53	67.47	21.19
SD	15.85	6.71	16.26	6.85	16.27	6.42	14.86	4.65
Range	32–91	12–36	37–94	12–39	42–96	12–34	34–86	12–32

QoL, Quality of Life; D, Depression.

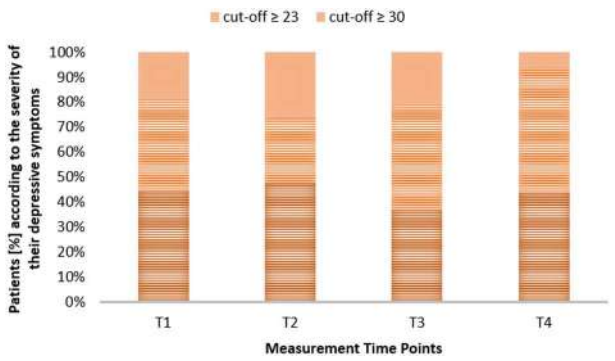

FIGURE 2 | Distribution of the patients depending on the severity of their symptoms over the measurement time points.

Psychosocial Adjustment Outcomes and Demographics

The group's ADI-12 mean scores are summarized in **Table 2**. The distribution of the patients (%) depending on the severity of their symptoms (not depressed, presence of any depressive disorder and major depression) are depicted in **Figure 2**. Mean scores of individual QoL are reported in **Table 2**.

There were no significant differences between the mean scores of the four measurements for both adjustment outcomes. Depression and quality of life mean scores remained constant over the measurement time points [ADI-12: $\chi^2_{(2,\ N=22)} = 4.64$, $p < 0.2$, Friedman Test; SEIQoL: $F(1,\ 14) = 0.61$, $p < 0.4$, repeated measures ANOVA]. Pairwise comparisons revealed however significantly lower ADI-12 scores at T4 (*Mdn* 20) than at T1 (*Mdn* 22.5) ($z = -2.4$, $p < 0.05$, Wilkoxon rank Test).

For each of the measurement time points we investigated the relationship between demographical aspects and adjustment outcomes. Age correlated significantly positive with QoL at T1 and T3 (T1: $r = 0.49$, $p < 0.01$; T3: $r = 0.51$, $p < 0.05$; Pearsons Correlations). No significant correlations were found between depression and age. For each of the measurement time points both depression and QoL did not differ between sexes and as a function of education (for statistical coefficients see Table 1 of Supplementary Materials).

Predictors of Psychosocial Adjutment: Descriptives and Longitudinal analysis

With mean scores ranging between 17.4 and 13.2 ALS-FRS values indicated high physical impairment of the patient sample. Average scores of ALS FRS and the illness duration (months since trying to spare their partners negative information and displaying strength and general good mood diagnosis) are summarized in **Table 3**. The average severity of the physical impairment increased significantly over time reflecting the degenerative character of the disease [$\chi^2_{(3,\ N=22)} = 13.08$, $p < 0.01$, Friedman Test].

Scores of received and perceived social support indicated a high and constant availability of social support in this sample (**Table 3**). No significant differences were found between the four time points [for perceived: $\chi^2_{(3,\ N=22)} = 1.4$, $p = 0.7$; for received: $\chi^2_{(3,\ N=22)} = 1.6$, $p = 0.6$; Friedman Tests]. Cohabitating patients showed on average high protective behavior by trying to spare their partners negative information and displaying strength and general good mood. Scores of protective buffering scale did not change over time [$\chi^2_{(3,\ N=22)} = 2.8$, $p = 0.4$; Friedman Test].

With respect to coping strategies, Friedman's ANOVA revealed significant differences between the frequencies of problem- and emotion-management strategies over the measurement time points. Wilcoxon signed-rank tests were used for pairwise comparisons (Bonferroni corrected) and indicated that, patients relied more frequently on both problem- and emotion- management strategies at T1 compared to the other time points. Whereas at T3 patients used less frequently emotion-management strategies. Scores of problem-appraisal and avoidant coping remained stable over time [for independence: $\chi 2_{(3,\ N=22)} = 5.75$, $p = 0.1$; for avoidance: $\chi^2_{(3,\ N=22)} = 0.76$, $p = 0.9$; Friedman Tests].

Mean scores of primary appraisals at all the measurement time points reflected that patients rated their illness situation as being rather threatening at T1, T2, and T4 (**Table 3**). Scores at T3 were significantly lower compared to all the other time points [$\chi^2_{(3,\ N=22)} = 7.6$, $p = 0.05$; Friedman Test], indicating that patients believed at this time point that their illness situation is not threatening at all. Moreover, patients constantly rated their own coping potentials as being high (for mean values see **Table 3**). This experienced high propensity to cope well with their disease did not change over time [$\chi^2_{(3,\ N=22)} = 4.9$, $p = 0.1$; Friedman Test].

At T1 significant mean differences were found between the appraisals of problem-focused coping potential and emotion-focused coping potential [$t_{(26)} = -4.5$, $p < 0.001$, Paired sample *t*-test], indicating that patients believed to deal better with the situation emotionally than by active attempts to change it.

TABLE 3 | Mean scores of model variables

		T1	T2	T3	T4
ILLNESS PARAMETERS					
ALS FRS	M/Mdn	17.4	15.9	14.4	13.2
	SD	9.8	10.1	10.1	11.1
	Range	0–36	0–36	0–35	0–34
	Maximum possible	40	40	40	40
Illness duration	M/Mdn	43.2	40.9	58.1	63.2
	SD	30.5	31.6	33.3	32.1
	Range	4–129	18–131	22–135	26–141
BSSS SCALES					
Perceived support	M/Mdn	29.6	28	29	29.3
	SD	3.9	5.5	3.8	3.4
	Range	17–32	14–32	19–32	22–31
	Maximum possible	32	32	32	32
Received support	M/Mdn	41.3	40	41.4	44.5
	SD	8.8	10.3	9.1	5.4
	Range	23–48	15–48	12-48	30-48
	Maximum possible	60	60	60	60
Search for support	M/Mdn	14.4	14.3	14.2	15.1
	SD	3.1	3.2	3.4	4.4
	Range	6-20	6-20	5-20	3-20
	Maximum possible	20	20	20	20
Need for support	M/Mdn	11.8	10.1	9.8	10.2
	SD	2.9	1.6	2.1	2.4
	Range	5-16	6-13	6-14	6-14
	Maximum possible	16	16	16	16
Protective buffering	M/Mdn	13.4	13.4	14.2	13.8
	SD	4.1	3.2	4.5	4.2
	Range	7-21	7-20	6-24	7-20
	Maximum possible	24	24	24	24
COPING STRATEGIES					
Problem management	M/Mdn	24.6	22.2	22.7	23.7
	SD	4.4	4.7	4.1	4.3
	Range	13-30	12-29	15-30	18-30
	Maximum possible	30	30	30	30
Problem appraisal	M/Mdn	20	18.9	18.5	20.3
	SD	4.6	5.2	3.1	2.9
	Range	10-25	7-25	12–23	14–23
	Maximum possible	25	25	25	25
Emotion management	M/Mdn	18	17.3	16.8	18.2
	SD	1.8	2.6	2.4	1.6
	Range	14–20	12–20	11–20	15–20
	Maximum possible	20	20	20	20
Emotional avoidance	M/Mdn	6.9	6	6.6	6
	SD	2.4	2.4	2.8	3.9
	Range	2–12	1–10	2–13	0–15
	Maximum possible	15	15	15	15
COGNITIVE APPRAISALS					
Appraisal of threat	M/Mdn	3.6	3.3	1.2	3.4
	SD	2.1	2.1	1.3	2.3
	Range	0–8	0–8	0–4	0–7
	Maximum possible	8	8	8	8

(Continued)

TABLE 3 | Continued

		T1	T2	T3	T4
Appraisal of coping potential	M/Mdn	5.83	5.91	5.3	6.5
	SD	1.7	1.7	1.9	1.4
	Range	2.5–9	2.5–8	2–8	4.5–9
	Maximum possible	9	9	9	9
Self-accountability	M/Mdn	1	1	4.9	1
	SD			2.04	
	Range	1–9	1–8	1–9	1–7
	Maximum possible	9	9	9	9
Other accountability	M/Mdn	1	1.5	2	1
	SD				
	Range	1–7	1–6	1–9	1–9
	Maximum possible	9	9	9	9
Future expectancy	M/Mdn	4.5	5.3	2	4.8
	SD	2.3	2.4		2.8
	Range	1–9	1–9	1–9	1–9
	Maximum possible	9	9	9	9

TABLE 4 | Summary of regression analysis of stress-coping variables at T1 predicting psychological adjustment to amyotrophic lateral sclerosis at T2.

Predictors	Dependent variables	Depression			Quality of life		
		B	SE B	ß	B	SE B	ß
Social support	Perceived social support	**−0.95**	**0.39**	**−0.44****	1.7	1.11	0.28
Cognitive appraisal	Appraisal of coping potential	**−2.30**	**0.69**	**−0.57****			
Coping strategies	Problem management				**3.2**	**1.45**	**0.42***
	Emotion management	0.09	0.69	0.02			
	Emotional avoidance				1.79	1.17	0.28
		$R^2 = 0.55$, $\Delta R^2 = 0.47$			$R^2 = 0.47$, $\Delta R^2 = 0.37$		
		$\boldsymbol{F_{(3,\ 23)} = 7.2, p = 0.002}$			$\boldsymbol{F_{(3,\ 23)} = 5.01, p = 0.01}$		

Bold values indicate statistically significant contribution in explaining the variance.
*$p < 0.01$; **$p < 0.05$.*

However, this difference could not be found for the other time points.

Regression Analyses

A regression was conducted to determine whether stress-coping model variables that were identified at T1 as being significant predictors continued to predict depression and respectively quality of life at T2. Results showed that 55% of the variance of severity of depressive symptoms at T2 was accounted for by all the T1 predictor variables taken together. The *b*-values (**Table 4**) indicated the independent contribution of each predictor to the total explained variance. Hence, perceived social support and appraisal of own coping potential individually accounted for a significant percentage in the variance in severity of depressive symptoms. Higher perceived social support [$t_{(22)} = 2.28$; $p < 0.05$] and more confidence in their own coping potential [$t_{(22)} = 2.49$; $p < 0.05$] predicted lower depressed mood. Similarly to T1, none of the coping strategies predicted the severity of depressive symptoms. Predictors that were selected at T1 continued to explain 47% of the variance in QoL at T2 [$F_{(3,\ 23)} = 5.01$; $p < 0.01$]. On the level of individual contributions, *b*-values indicated only for problem management coping strategies significant results. Patients who searched more frequently for information and support reported higher QoL. Results are depicted in **Figure 3**.

Cross-sectional regression analyses revealed that at T2 neither severity of depressive symptoms nor QoL could be predicted by the degree of physical impairment and illness duration. A summary of the regression analyses is presented in **Table 5**. Depression was significantly predicted by cognitive appraisals. Appraisal of own coping potential significantly contributed to explaining portions of the total variance of depression scores, higher appraisal of own coping potential predicting lower severity of depressive symptoms. The variance of depression scores could not be significantly accounted for by any of the coping and social support scales. On the contrary, higher social support significantly predicted higher quality of life values. The independent contribution of protective buffering scale to the total explained variance of the quality of life scores was significant. Coping strategies did account for a significant amount of the variance of quality of life, with problem management strategies (seek for information and support) being most predictive.

However, this relation did not reach significance at the corrected *p*-value. Likewise, none of the appraisal scales could significantly predict quality of life.

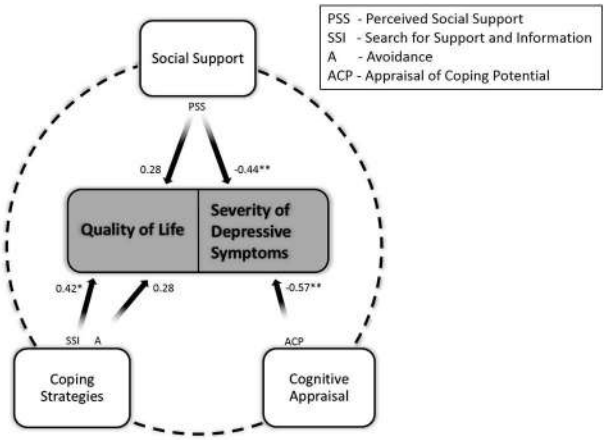

FIGURE 3 | The modified stress-coping model of psychosocial adjustment to amyotrophic lateral sclerosis on the basis of longitudinal regression analyses. The psychosocial predictor variables at T1 accounted together for a considerable amount of variance in both outcomes of psychosocial adjustment (depression and quality of life) at T2. This is illustrated by the dashed line. Variables that displayed independent predictive power are denoted by stars.

Discussion

Short and Long-term Psychosocial Adjustment to ALS

For our longitudinal study the adaptation of Lazarian stress-coping theory to chronic illness and disabilities (Pakenham, 1999) has shaped the foundation for identifying determinants of adjustment to ALS. Longitudinal regression analysis showed that significant predictors of adjustment outcomes, as found at T1 (Matuz et al., 2010), continued to predict to a large extent adjustment at T2. Perceived social support together with appraisal of one's own coping potential and independence explained 55% of the variance of severity of depressive symptoms. Perceived social support, seek for information and support and avoidance accounted for 47% of the variance in quality of life indices.

We characterized predictive factors for favorable adjustment to ALS over time. The pattern of the longitudinal results indicated stable depressive symptoms and quality of life indices reflecting a successful adjustment to the disease across four measurement time points during a period of about 2 years. Although the sample reported on average low depressive symptoms and high quality of life, considerable variability in the severity of depressive symptoms and quality of life scores across persons and time was apparent. These results are in line with the existing evidences from previous research on psychological aspects in ALS (Rabkin et al., 2005, 2015; Lulé et al., 2008; McElhiney et al., 2009). Several

TABLE 5 | Summary of regression analyses on the two adjustment variables with the subscales of each stress–coping predictors separately at T2.

Predictors	Dependent variables	Depression			Quality of life		
		B	SE B	ß	B	SE B	ß
Social support	Perceived	−0.65	0.41	−0.51	1.08	1.12	0.30
	Received	0.12	.22	−0.17	0.85	0.48	0.53
	Protective buffering	**1.14**	**0.46**	**0.53***	**−2.27**	**0.96**	**−0.46***
		$R^2 = 0.32$, $\Delta R^2 = 0.20$			$R^2 = 0.45$, $\Delta R^2 = 0.35$		
		$F_{(3, 17)} = 2.7, p = 0.07$			**$F_{(3, 17)} = 6.2, p = 0.005$**		
Cognitive appraisal	Primary appraisal	−0.48	0.62	−0.15	0.26	1.92	0.03
	Appraisal of coping potential	**−2.84**	**0.78**	**−0.69****	3.89	2.67	0.38
		$R^2 = 0.42$, $\Delta R^2 = 0.36$			$R^2 = 0.13$, $\Delta R^2 = 0.03$		
		$F_{(2, 19)} = 6.9, p = 0.006$			$F_{(2, 18)} = 1.3, p = 0.2$		
Coping strategies	Problem management	0.42	0.80	0.14	3.5	1.87	0.48
	Problem appraisal	−1.17	1.05	−0.44	−0.65	2.38	−0.09
	Emotion management	−0.64	0.98	−0.24	2.22	2.14	0.35
	Emotional avoidance	0.003	0.74	0.001	−0.85	1.67	−0.13
		$R^2 = 0.38$, $\Delta R^2 = 0.24$			$R^2 = 0.46$, $\Delta R^2 = 0.33$		
		$F_{(4, 17)} = 2.6, p = 0.07$			**$F_{(4, 16)} = 3.4, p = 0.03$**		
Illness parameters	Physical impairment	0.05	0.16	0.08	−0.21	0.39	−0.13
	Time since diagnosis	0.02	0.05	0.12	0.07	0.13	0.13
		$R^2 = 0.01$, $\Delta R^2 = -0.08$			$R^2 = 0.04$, $\Delta R^2 = -0.06$		
		$F_{(2, 19)} = 0.14, p = 0.8$			$F_{(2, 18)} = 0.37, p = 0.7$		

Bold values indicate statistically significant contribution in explaining the variance.
*$p < 0.01$; **$p < 0.05$.*

studies showed that many individuals with ALS report good adjustment, however, evidence for heterogeneity in trajectories of adjustment across individuals and time have also been shown (Pagnini, 2013). Differences between depression scores at T1 and T4 in our sample suggest that people with ALS can eventually hone their adjustment over time. The mechanisms which are responsible for this improvement are still not clear, however, it is possible that people with ALS apply strategies as described by the so called TOTE model (Miller et al., 1986). According to this, individuals first test for the presence of a difference between their expectations and their current experiences and then engage in various actions to reduce this difference. Coping strategies are here important mediators. The difference is then tested again, and the cycle iterates until expectations and experiences match. For the case of people with ALS it has been previously argued that as the disease progresses patients might reshape and redefine their expectations so that these match with their ongoing experience and thus leading to less negative feelings and higher quality of life (Real et al., 2014). Future research is nevertheless needed to address this issue explicitly for example by clustering and characterizing adaptors and non-adaptors across time.

On the level of individual contributions we found that higher perceived social support and appraisal of own coping potential continued to significantly predict lower depressive symptoms. Likewise, more frequent use of problem management coping strategies, such as seeking for support and information continued to predict higher quality of life.

Social support has been shown to affect adaptive outcomes through cognitive, emotional, and physiological pathways (Wills and Fegan, 2001). A supportive, uncritical social environment can help patients use effective coping strategies, encourage positive health behaviors, and diminish physiological reactivity to stress. For ALS, research has repeatedly underlined the importance of social networks, familiar support, and availability of technological aid devices (Chió et al., 2004; Goldstein et al., 2006; McLeod and Clarke, 2007; Olsson et al., 2010; Tramonti et al., 2012). Our results indicate that perceived social support, which reflects patients view about the quantity and quality of the support received, successfully predicted depressive symptoms over time. Severity of depressive symptoms can be obviously well-predicted in ALS by cognitive appraisal processes. Our results further support this statement by showing that patients perceiving their own coping potential as high experienced lower severity of depressive symptoms across time points.

Similar to our previous outcomes of the cross sectional analysis (Matuz et al., 2010) revealed that none of the coping strategies did predict severity of depressive symptoms over time. Coping had rather an effect on quality of life. Search for information and support significantly predicted high quality of life over time. Problem focused coping attempts have been repeatedly reported as being more adaptive for patients with chronic diseases (Young, 1992; Keefe et al., 2002; Savelkoul et al., 2003) and to some extent for ALS patients as well (Montel et al., 2012).

Avoidant coping has on the contrary lost its predictive power for quality of life at T2. Coping strategies people employ and their utility are likely to vary as the adaptive tasks of illness change (Blalock et al., 1993). For example, breast cancer patients who reported frequent use of cognitive avoidance prior to breast biopsy showed less distress at that point, however, higher distress scores after cancer diagnosis and after surgery (Stanton and Snider, 1993; Lutgendorf et al., 2002; Hack and Degner, 2004). Avoidant coping strategies may be useful at acute points of specific crisis in the progress of the illness, however, over time avoidance is typically related to maladjustment. Based on our results this seems to be true also for ALS. It may prevent them from taking measures necessary for coping with the disease in the future, such as seeking information about assistive technology for communication or artificial nutrition.

Unexpectedly, perceived social support did not continue to predict quality of life at T2. Consequences of chronic disease can be abrupt and distinctive (e.g., surgeries, progression of specific symptoms), or they can be rather gradual (e.g., declines in vitality, social contacts) (Thompson and Kyle, 2000). Changes in patients' social relations and networks can proceed with an uneven course (Stanton et al., 2007) shaping the interaction between social support and adjustment outcomes. The current cross-sectional results at T2 support this notion by revealing significant contribution of social support in explaining the variance of quality of life indices, yet this time by the individual contribution of the subscale protective buffering. Thus, people with ALS manifesting more protective behavior toward their partners, e.g., withholding bad news, showing more strength experience higher quality of life. Whereas partners' overprotection (including protective buffering) is considered an unsupportive behavior (Schokker et al., 2010; Vilchinsky et al., 2011), patients' protective buffering acts toward their partners and their positive effects on adjustment received little attention in the literature. Being more protective with their partners presumably helps ALS patients in reducing their own perception of being a burden and eventually increases their perception of self-efficacy.

Last but not least, cross sectional regression revealed that none of the adjustment outcomes could be significantly predicted by illness parameters. Severe functional impairment as well as ALS duration are not necessarily related to poorer quality of life and depressive mood. With these results we contribute to the still ongoing debate among ALS care specialists over the role of severity of physical impairment and illness related characteristics in maintaining mental health and quality of life in people with ALS. Our both cross sectional and longitudinal findings indicate that psychosocial aspects are better predictors of adjustment to ALS than illness related characteristics.

Implications for Clinical and Home Healthcare

Overall, the analyses presented here extend the literature on psychological aspects in ALS and can guide psychological interventions developed for people with ALS.

Although mainly limited by the sample size and the drop outs due to death and illness progression, our results enriched the understanding of psychosocial adjustment to ALS. Empirical evidence is provided for the predictive utility of the adaptation of the stress-coping model in finding those factors that promote or hinder psychosocial adjustment to ALS. Also, the current study contributes to a better conceptualization of adjustment, showing

that ALS necessitates adjustment in multiple life domains as the diseases advances.

Existing psychological interventions in ALS can be rendered more efficacious by including the current findings. Whereas cognitive therapeutic strategies targeting appraisal of coping potential and available social resources can be more efficient for depression, behavioral therapy directed toward coping effectiveness training could improve quality of life in ALS. Moreover, dyadic interactions should receive more attention, specifically about reciprocal protective buffering behavior that could assist couples in coping with the challenges faced during illness.

Limitations

The main limitations of the present study are related to the small sample size which over time due to drop outs lead to an inadequate predictors:sample size ratio for regression modeling at the last two time points. The generalizability of the results should be therefore considered with caution. Moreover, some of the used measures showing moderately strong psychometrical characteristics pose limitations. Finally, due to a relative high variability and wide range of the time between the measurement time points (3–6 months), which were unavoidable for clinical and organizational reasons results should be interpreted with caution. In future studies more information about dropouts would be desirable to ensure that not only those who manage to adjust well remain in the sample.

Conclusions

Despite these limitations we conclude that psychological strategies exist to cope well with ALS—against all odds—and effort should be invested toward improving support instead of further legalizing euthanasia. The here presented data and all previous work on QoL and psychological aspects in ALS from our group (Lulé et al., 2008, 2011, 2014; Matuz et al., 2010; Real et al., 2014) as well as from other groups clearly disprove the widespread prejudice of a negative QoL and high depression in all stages of ALS and strongly support a palliative approach to ALS which equally implies advice with regards to coping strategies, provides reasonable amount of illness and support related information at any one time and heartens patients to seek social support.

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Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fpsyg.2015.01197

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