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Title: Impact of disease, cognitive and behavioural factors on caregiver outcome in Amyotrophic Lateral Sclerosis

Running title: Impact of ALS on caregivers

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Objective

Up to 50% of patients with Amyotrophic Lateral Sclerosis (ALS) show mild to moderate cognitive–behavioural change alongside their progressive functional impairment. This study examines the relative impact of patients' disease symptoms, behavioural change and current executive function and social cognition abilities on psychosocial outcomes in spouse caregivers of people with ALS.

Methods

Thirty–five spouse caregivers rated their own levels of depression and anxiety, subjective burden and marital satisfaction. Caregivers also rated their partner's everyday behaviour. The patients were assessed for disease severity and cognitive function, with composite scores derived for executive function and social cognition.

Results

Regression analyses revealed that caregiver burden was predicted by the severity of patients' limb involvement and behavioural problems. Depression was predicted by patients' limb involvement, while behavioural problems and patient age predicted caregiver anxiety. Current marital satisfaction was predicted by patient behavioural problems beyond the level of pre–illness marital satisfaction.

Conclusions

The study highlights the potential impact of ALS patients' functional impairment and behavioural change on ALS caregivers' psychosocial functioning. Clinical communication with ALS families should emphasise both physical and psychological challenges presented by the disease.

Keywords: cognitive–behavioural impairment, disease severity, anxiety, depression, caregiver burden.

Introduction

While less marked than observed in frontotemporal dementia (FTD), up to 50% of non–demented patients with Amyotrophic Lateral Sclerosis (ALS) may show behavioural symptoms (1) including apathy, disinhibition and/or egocentrism (2–4). In addition, non–demented people with ALS may also show impaired performance on standardised tasks of executive function (5) and social cognition (6–9). In informal family caregivers, mood and subjective burden is affected by the patients' functional impairment (10–12) and the presence of behavioural change (13–15). However, the contribution of cognitive impairment, as assessed by standardised tests, is unclear. The current study sought to explore the relative impact of patient disease, objective cognitive function and behavioural change on four indicators of caregiver outcome: depression, anxiety, burden and marital satisfaction.

Material and Methods

Participants

Spouse caregivers were recruited as part of a parallel study which explored cognitive and behavioural change in non–demented patients with ALS (for information about this study see Supplementary Appendix Table S1). Participants were recruited between January 2011 and May 2013 from five Motor Neurone Disease Care and Research Centres in the UK. The following exclusion criteria were applied for all participants: a diagnosis of a psychiatric condition; a formal diagnosis of dementia; a first language other than English. Patients were excluded from the parallel study on the basis of a formal diagnosis of another neurological condition or diabetes; aged > 75 years and evidence of respiratory insufficiency, as determined by the patients' clinical team; a forced vital capacity (FVC) < 70% (where available) and a score > 10 on the Epworth Sleepiness Scale (16). In total, 46 caregivers were approached with approval of the patient with ALS. Nine declined, and one was excluded due

to dementia. One carer was excluded as they could not provide a report on their relationship prior to their spouse's illness. Informed written consent was obtained from the remaining 35 caregivers and their spouses. Ethics approval was obtained from the National Research Ethics South East London Research Ethics Committee 4 (11/H0807/1; dated 22/03/2011).

Measures

Caregiver outcome

The Hospital Anxiety and Depression Scale (HADS) (17) was used to measure caregiver anxiety (HADS A) and depression (HADS D). The Zarit Burden Inventory (ZBI) (18) measured caregivers' perceived burden associated with their partner's illness and their caregiving role. Caregivers' perceived marital satisfaction was measured using the Marital Intimacy Scale (MIS) (19), which assesses several dimensions of the marital relationship, such as affection, compatibility and autonomy. Caregivers completed this measure with respect to the time of the interview (MIS current) and a time approximately two years before the onset of their partner's ALS (MIS pre–illness).

ALS measures

Physical symptom severity was assessed using the Revised Amyotrophic Lateral Sclerosis Scale (ALSFRS–R) (20). Patients' mood was measured using the revised HADS (HADS-R), which removes two items that may be confounded with the physical impairment of ALS (21). Cognitive function was assessed on a range of neuropsychological tests of executive function and social cognition. Table 1 provides descriptions and references (22-27) for these tasks. To reduce the number of variables used in the analyses, composite scores were created as follows: test scores were standardised by subtracting the mean score of the control group from each participant's score on an individual test and then dividing the difference by the corresponding standard deviation of the control group. The resulting standardised scores were

then summed according to theorized function and divided by the number of component tests contributing to the composite. When participants did not complete all measures in the composite, the measures that were completed were standardised and averaged as above. Where necessary, scores were reflected so that they shared the same direction; a higher score represented poorer performance. Internal consistency for these composites for the patient group (n=35) were satisfactory (Executive function composite α=.79; Social cognition composite α=.89). Caregivers rated their partner's current behaviour using the informant version of the Frontal Systems Behavioural Scale (FrSBe) (28) (apathy, disinhibition and everyday behavioural indications of executive dysfunction) and emotional lability using the Emotional Lability Questionnaire (ELQ) (29).

Data Analysis

Data were analysed using IBM SPSS for Windows version 21 (IBM SPSS Statistics Armonk, NY, USA). Demographic, clinical and cognitive characteristics were reported as percentages for categorical data and means for continuous variables. Categorical data were analysed using Chi–square tests. Outliers were identified and transformed by recoding the outlying value with a score one unit higher/lower than the next highest/lowest non–outlying score in the distribution. Pearson's correlations and multiple regression analyses were used to examine the relationships between parameter and caregiver outcome variables. All tests were two–tailed, and statistical significance was set at $p < 0.05$.

Results

ALS sample characteristics

Patients' demographics and disease information are shown in Table 2. Limb onset disease was observed in 77.1% and bulbar onset in the remainder. Most patients (80%) were receiving treatment with riluzole. Table 3 shows patients' mood scores, cognitive composite scores, mean group performance on individual cognitive tests and the percentage of patients whose performance was at or lower than the 5th percentile of an age-, education-, gender-matched control sample from a larger parallel study (see Supplementary Appendix Table S1). Table 3 also shows caregiver ratings of patient behavioural involvement and emotional lability. The percentage of patients being endorsed by their caregivers as demonstrating clinically relevant behaviour (a T-score > 65 on the FrSBe domains) is also shown. Figure 1 presents the proportion of patients by number of impaired scores on the cognitive tasks (as defined as a score at or lower than 5th percentile of controls' scores) and behaviour domains (as defined by T-Score >65). The number of patients meeting current cognitive impairment criteria (30) (impairments on two or more tests of executive function) was 3/35 (8.6%). By extension, the number of impairments on two or more domains of social cognition was 4/35 (11.4%). The number of patients meeting criteria for impairment on two or more domains of the FrSBe was 8/33 (24.2%).

Caregiver sample characteristics

The mean age of the caregiver group was 57.7 years (SD = 10.5) and 71.4% were female. The mean duration of their marriage to the patient was 33.2 years (SD = 13). Table 4 shows levels of caregiver anxiety, depression, burden and marital satisfaction (current and pre–illness). Pre–illness MIS ratings (M = 76.1, SD = 15.4) were significantly higher than current MIS ratings (M = 70.2, SD = 18.4), $t(31) = 3.04$, $p = 0.005$, $d = 0.35$. Current and pre–illness MIS scores were highly correlated ($r = 0.81$, $p < 0.001$).

Predictors of caregiver outcome

Potential predictor variables were selected on the basis of past research (10–15) and the objectives of the study and comprised ALSFRS–R subscale scores; months since diagnosis; Executive and Social Cognition composite scores; FrSBe Total and subscale T–scores; ELQ total severity score; caregivers' age; patients' age, patients' HADS-R scores and years of marriage. Variables which showed significant paired associations with the outcomes ($p < 0.05$) were entered into forward selection multiple regressions (Table 5). The correlations between outcome measures are shown in the Supplementary Appendix S2.

Caregiver depression: Significant correlates of caregiver HADS D were ALSFRS–R Limb ($r = -0.48$, $p = 0.004$, $n = 35$), FrSBe Apathy ($r = 0.43$, $p = 0.01$, $n = 33$) and FrSBe Total ($r = 0.37$, $p = 0.04$, $n = 33$). Only ALSFRS–R Limb entered the final model ($F(1,31) = 8.07$, $p = 0.08$) explaining 18% of the variance, with greater functional impairment (lower ALSFRS–R limb scores) associated with higher caregiver depression (higher HADS D scores).

Caregiver anxiety: Significant correlates of caregiver HADS A were FrSBe Total ($r = 0.40$, $p = 0.02$, $n = 33$), ELQ Total ($r = 0.36$, $p = 0.03$, $n = 34$), patients' age ($r = -0.4$, $p = 0.03$, $n = 35$) and ALSFRS–R Limb ($r = -0.38$, $p = 0.03$, $n = 35$). FrSBe Total and patients' age remained in the model ($F(1,30) = 5.4$, $p = 0.01$), explaining 22% of anxiety variance. Greater carer anxiety (higher HADS A scores) was predicted by greater behavioural impairment (higher FrSBe Total scores) and younger patient age.

Caregiver burden: Significant correlates of the ZBI score were ALSFRS–R Limb ($r = -0.66$, $p = <0.001$, $n = 34$), FrSBe Apathy ($r = 0.63$, $p <0.001$, $n = 32$), FrSBe Disinhibition ($r = 0.51$, $p = 0.003$, $n = 32$), FrSBe Executive Dysfunction ($r = 0.51$, $p = 0.003$, $n = 32$), FrSBe

Total ($r = 0.69$, $p < 0.001$, $n = 32$) and patients' age ($r = -0.35$, $p = 0.04$, $n = 34$). ALSFRS–R Limb and the FrSBe Total remained in the model ($F(2,28) = 80.7$, $p < 0.001$) and explained 84% of the variance in caregiver burden. Caregiver burden increased with worsening physical impairment (lower ALSFRS–R limb scores) and behavioural problems (higher FrSBe Total scores) in the person with ALS.

Current caregiver marital satisfaction: Significant correlates of current MIS scores were FrSBe Apathy ($r = -0.37$, $p = 0.04$, $n = 31$), FrSBe Executive Dysfunction ($r = -0.49$, $p = 0.005$, $n = 31$) and FrSBe Total ($r = -0.54$, $p = 0.002$, $n = 31$). Only FrSBe Total entered the model, $R^2 = 0.30$, adjusted $R^2 = 0.27$, $F(1,29) = 12.12$, $p = 0.002$, standardised $\beta = -0.54$, $t(29) = -3.48$, $p = 0.002$. To control for the possible influence of pre–illness marital satisfaction FrSBe Total scores were then entered into a hierarchical regression analysis, controlling for pre–illness MIS scores. The model explained 78% of the variance in caregivers' current marital satisfaction ($F(2,27) = 52.7$, $p < 0.001$) with FrSBe Total scores remaining a significant independent predictor.

Selection bias

Caregivers were invited to the study on the condition that their partner with ALS took part in a larger study (see Supplementary Appendix Table S1) and consented to their spouse being approached. Data for the 9 spouses who declined invitation are not available; however, the demographic, disease and cognitive profiles of the 9 patients (n = 2 female) whose spouses declined participation are shown in Table S3 in the Supplementary Appendix.

Discussion

Previous studies have highlighted the impact of disease factors (10–12) and behavioural change (13–15) on caregivers of ALS, but the contribution of objectively measured patient cognition function has not been established. The present results suggest that formal measures of executive function and social cognition do not independently predict any of the caregiver outcomes assessed. This is in contrast to previous studies of caregivers of patients with dementia (31), but similar to reports of caregivers of patients with Mild Cognitive Impairment (32). Together, such evidence suggests that for caregivers of non–demented patients (including ALS) the *perceived* severity of patients' everyday behavioural impairment (as reflected in FrSBe ratings) have a greater effect on caregiver well–being than the objective level of cognitive impairment. However, the profile of cognitive impairments in the current patient sample may have influenced the results obtained. While impairments in performance on some measures of executive function and social cognition were noted in some patients, only a small proportion of patients qualified for cognitive impairment according to Strong et al's criteria. Thus, patients' cognitive deficits might not have been severe enough to interfere with their everyday actives or create burden for their caregiver. With progression, and worsening of cognitive function in some patients, caregivers may become more aware of and affected by cognitive impairment and its impact on daily function.

Slightly different predictors emerged for caregiver burden, depression and anxiety, although the differences in the models should be interpreted with caution. Of the ALS symptoms, the severity of limb involvement was the best predictor of caregiver burden and depression, at least in the present sample of patients relatively early in their disease. Functional impairment may lead to increased physical dependence on the caregiver, imposing restrictions upon caregivers' personal and social activities and needs (13, 33). With disease progression and

potential worsening of bulbar and respiratory impairments, these other symptoms may become more important for caregiver outcomes. Recent studies have emphasised the importance of the behavioural above the physical aspects of ALS on caregivers (14, 15). In contrast, the current results suggest that *both* patients' physical and behavioural symptoms may act in concert in their impact on caregivers. The disparity in these findings might reflect differences in the patient samples in terms of the severity of ALS and behavioural symptoms. For example, perhaps responding to acute behavioural symptoms eventually dominates caregivers' priorities even alongside the progression of the patient's disability.

As in previous studies, greater behavioural symptoms as measured by the FrSBe predicted poorer outcome in terms of burden, anxiety and marital satisfaction, even in spouses of patients in the first two years from diagnosis. This highlights the importance of detection of such problems early in the disease trajectory. The FrSBe Total score was a better predictor of caregiver outcome than the subscale scores, suggesting that global behavioural change may be a more useful indicator than individual behavioural symptoms for caregivers of non–demented patients. This was true for the current sample despite more than half of the patients being endorsed for clinically relevant levels of apathy. Demographic characteristics did not emerge as independent predictors with the exception of patient age, with higher anxiety scores seen in the caregivers of younger patients. This may reflect concerns about the future in younger couples where the ALS may have greater economic and wider family impact.

Caregivers' levels of perceived marital satisfaction were significantly reduced compared to those reported for the period before their partners' illness, replicating previous findings (34). However, the quality of the marital relationship prior to the onset of the ALS remained the most important determinant of current satisfaction. The significant association between

marital satisfaction and burden suggests that a poor pre–illness relationship increases the risk of greater burden in caregivers after the onset of ALS, or conversely, that a strong relationship is protective against the negative effects on caregiver outcome.

Caregivers have reported that clinical services place disproportionate focus on the practical rather than emotional adjustments to the disease (35, 36). The current findings suggest that routine monitoring of the patient's functional, cognitive and behavioural status may prepare the clinical team better to tailor their support for caregivers. Early interventions could include educating the caregiver about the possible interpersonal or behavioural changes that might accompany their partner's disability, so that caregivers do not misinterpret their partner's emerging disposition as resulting from inherent problems within their relationship (37). More formally, caregivers might benefit from group or individual psychosocial interventions, although, to date, none have been evaluated for potential efficacy in improving the wellbeing of ALS caregivers.

This study is limited by its cross–sectional design; a longitudinal study of caregiver outcomes alongside patients' declining functional status and behavioural change would further clarify the causal relationships and interactions between the measures as the ALS progresses. Although objective measures of patients' neuropsychological performance were not predictive of caregiver outcomes here, there is merit in investigating whether changes in cognitive indices over time explain variability in caregiving outcomes at different stages of disease. As already mentioned, the relatively preserved cognitive status of the majority of patients in the sample may limit the inferences drawn regarding the influence of ALS-related cognitive impairment on caregivers' wellbeing. Future research would benefit from including a more cognitively heterogeneous sample and/or comparisons between caregivers of "pure

ALS" and ALS-FTD. The use of composite scores to measure patients' cognitive functions may have underestimated or masked correlations for individual measures; however, these were necessary to allow parsimonious analyses for the small sample size. The HADS is not diagnostic of mood disorder and caregivers' mean values for anxiety and depression did not suggest the presence of generally clinically significant dysthymia. Thus, the generalisability of these results to clinically depressed or anxious caregivers is restricted. The lack of objective FVC scores for some patients means that the study may underestimate the influence of subtle respiratory deficits (not noticeable to the patient or the clinical team) on patients' cognitive performance and/or caregivers' outcomes. The influence of recall bias on measures assessing retrospective outcomes cannot be excluded. Following ethical guidelines, the study could not record data from the nine spouses who declined to consent to the research and thus we cannot exclude the possibility of selection bias. Finally, this study emphasised caregivers' experiences and precludes comment on the impact of ALS on patients and their spouses as a dyadic unit. Nonetheless, the current findings implicate the roles of both patients' functional impairment and behavioural dysfunction in caregivers' responses to ALS. Our findings suggest, therefore, that clinical communication with ALS families should emphasise both the physical and psychological challenges presented by the cognitive–behavioural features of ALS.

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Declaration of conflicting interests

None

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Table 1 Descriptions of Executive Function and Social Cognition Tasks

Task	Description	Scoring
The verbal fluency index (22)	Participants write down/say as many words as possible in a given time limit and under conditions in which the response is specified by a particular restriction, such as a letter. In this study participants had to produce as many words beginning with S as they could in five minutes and as many 4–letter words beginning with C in four minutes. In a subsequent control condition the participant copies/reads out these words as quickly as they can.	An index is calculated by subtracting the time taken to copy/read aloud the words from the duration of the word generation condition and dividing this by the total number of words generated. This index represents the average time taken to generate each word; higher scores indicating longer thinking times and greater executive impairment.
The Card Sorting task from the Delis–Kaplan Executive Function Scale (23)	Participants sort cards into mutually exclusive categories based on the verbal or visual information of the cards with the goal of making as many sorts as possible. Participants are required to describe the conceptual relationships between cards within each created category.	The maximum possible scores (32 for number of sorts made; 64 for description scores) minus the participant's score served as a measure of 'errors' on these conditions; the higher these scores, the worse the performance on these conditions.
The Brixton Spatial Anticipation test (24)	Participants are presented with series of arrays containing 10 circles. Each array contains one coloured circle, the position of which varies from one array to the next according to implicit rules (which change abruptly). Participants indicate the likely position of the coloured circle in the following array.	The outcome measure was the total number of errors, with higher scores indicating worse performance (maximum possible errors were 56)
Three subtests of The Awareness of Social Inference Test (TASIT) (25)	These tasks use enacted scenes of everyday social interaction: Emotional Evaluation (EET, dynamic videos of basic emotion expression); Social Inference–minimal (SIM–M, dynamic videos portraying sincere and sarcastic social exchanges); Social Inference–enriched (SI–E, dynamic videos portraying sincere, sarcastic and deceptive social exchanges)	The maximum possible scores (EET: 28; SI–M: 60; SI–E: 64) minus the participant's scores on each subtask served as a measure of 'errors'; the higher the scores, the worse the performance.

Three subtests of the Happé Cartoon and Scenarios Task (26)	These tasks use humorous cartoons and vignettes depicting characters in social situations involving deception, belief and intention. In the experimental conditions, the targeted inference related to the mental states of these characters. In control conditions, the targeted inference related to physical causation or logical sequence.	The maximum possible scores (cartoon task 1: 32; cartoon task 2: 30; vignettes: 32) minus the participant's score served as a measure of 'errors'; the higher these scores the worse the performances.
The Reading in Mind in the Eyes (RME) task (27)	Participants are required to attribute complex mental or emotional states to facial images depicting only the eye region.	The maximum score (36) minus the participant's score served as a measure of 'errors'; the higher the score the worse the performance.

Table 2 Patient demographics and disease information

	Mean	SD	Min - Max
Age	60.9	8.4	32.0 - 80.0
Education (years)	14.2	3.6	10.0 - 24.0
Months since symptom onset	30.4	14.3	10.0 - 75.0
Months since diagnosis	14.8	12.2	3.0 - 51.0
Age at symptom onset	58.6	8.5	34.0 - 72.0
ALFSFRS–R total severity score (max 48)	34.1	8.2	9.0 - 48.0
ALSFRS–R bulbar severity score (max 12)	9.3	3.0	1.0 - 12.0
ALSFRS–R Limb severity score (max 12)	14.0	6.0	3.0 - 24.0
ALSFRS–R Respiratory severity score (max 12)	10.8	2.0	2.0 - 12.0
Epworth Sleepiness Scale Score (max 24)	3.3	2.9	0.0 - 10.0

Min, minimum; Max, maximum; ALSFRS–R, Amyotrophic Lateral Sclerosis Functional Rating Scale: bulbar = items 1–3; Limb = items 4–9; respiratory = items 10–12, lower scores indicate greater functional impairment.

Table 3 Mood, cognitive performance and behaviour of ALS participants

Measure	Mean	SD	Min-Max	N	Cut-off	No. (%)[a]
HADS-R Depression score	2.5	2.1	0.0-9.0	35	8	1 (2.9)
HADS-R Anxiety score	4.3	3.7	0.0-18.0	35	9	5 (14.3)
Executive Function Composite	0.5	0.4	-0.5-3.3	35	1.6	5 (14.3)
Social Cognition Composite	0.4	0.8	-0.9-2.9	35	1.7	4 (11.4)
VFI – S words	5.3	3.3	0.9-14.4	35	8.6	6 (17.1)
VFI – C words	16.2	12.0	0.04-39.3	35	20.7	3 (8.6)
DKEFS Card Sorting	6.3	2.1	2-10	33	12	2 (6.1)
DKEFS Card Sorting Description	28.5	11.3	8-54	33	47	3 (9.1)
Brixton errors	18.1	5.4	7-30	35	29.5	2 (5.7)
TASIT Emotion Evaluation Test	6.1	2.8	2-13	35	11	3 (8.6)
TASIT Social Inference Minimal	11.1	7.6	0-33	35	17	7 (20)
TASIT Social Inference Enriched	12.3	6.2	4-29	35	25	1 (2.9)
Happé Cartoons task 1	11.9	5.7	1-24	29	20.6	3 (10.3)
Happé Cartoons task 2	12.2	4.7	2-21	29	18.6	0 (0)
Happé Scenarios	9.2	4.1	1-17	25	19.1	0 (0)
RME	11.9	4.8	4-21	34	17	4 (11.8)
FrSBe Total	63.7	12.8	42-107	33	65	11 (33.3)
FrSBe Apathy	69.2	13.6	46-94	33	65	19 (57.6)
FrSBe Disinhibition	55.0	11.8	39-88	33	65	5 (15.2)
FrSBe Executive Dysfunction	60.0	13.3	41-102	33	65	10 (30.3)
ELQ Total	5.0[b]	0.0-15.5[c]	0.0-43.0	34	21	6 (17.6)

Higher scores indicate worse mood, cognitive performance and greater behavioural impairment and greater emotional lability. [a]Number and percentage of patients meeting cut-

off criteria for ‘caseness’ (HADS-R); performance at or below 5th percentile of controls (composites, cognitive tests scores and ELQ) and clinically relevant behaviour (FrSBe); [b]Median; [c]IQR.

Table 4 Caregivers' self–ratings for outcomes

Caregiver self–report measures	**Scores**	**Mean**	**SD**	**N**
The Hospital Anxiety and Depression Scale (HADS)(17)	HADS A	9.2	4.6	35
	HADS D	5.7	4.0	35
The Zarit Burden Interview (ZBI)(18)	ZBI Total	29.4	14.1	34
The Marital Intimacy Scale (MIS)(19)	MIS pre–ALS	76.1	5.4	32
	MIS current	70.2	18.4	32

Higher scores indicate worse symptoms except for the MIS measure in which higher scores indicate greater marital satisfaction.

Table 5 Predictors of caregivers' outcomes

	Model 1				Model 2			
Outcome Predictor	**R^2**	**Adj. R^2**	**β**	**p**	**R^2**	**Adj. R^2**	**β**	**p**
Depression								
ALSFRS–R Limb	0.21	0.18	-0.45	<0.01				
Anxiety								
FrSBe Tot.	0.16	0.13	0.40	0.02	0.27	0.22	0.35	0.04
Patients' age (years)							-0.34	0.04
Burden								
FrSBe Tot.	0.60	0.59	0.78	<0.01	0.85	0.84	0.69	<0.01
ALSFRS–R Limb							-0.51	<0.01
Marital Intimacy								
MIS pre–illness	0.63	0.62	0.80	<0.01	0.80	0.78	0.68	<0.01
FrSBe Tot.							-0.42	<0.01

Table displays output for forward regression analyses except for Marital Intimacy which is a hierarchical regression analysis. Adj., Adjusted; β, standardised beta; ALSFRS–R Limb, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised Limb subscale; FrSBe Tot., Frontal Systems Behaviour Scale Total T score; MIS pre–illness, Marital Intimacy Scale score rated for period two years prior to ALS onset.

Table 1 Descriptions of Executive Function and Social Cognition Tasks

Table 2 Patient demographics and disease information

Min, minimum; Max, maximum; ALSFRS–R, Amyotrophic Lateral Sclerosis Functional Rating Scale: bulbar = items 1–3; Limb = items 4–9; respiratory = items 10–12, lower scores indicate greater functional impairment.

Table 3 Mood, cognitive performance and behaviour of ALS participants

Higher scores indicate worse mood, cognitive performance and greater behavioural impairment. [a] Number and percentage of patients meeting cut-off criteria for 'caseness' (HADS-R), performance at or below 5th percentile of controls (composites and cognitive tests scores) and clinically relevant behaviour (FrSBe); [b]No cut-off score has been established for ELQ; [c]Median; [d]IQR.

Table 4 Caregivers' self–ratings for outcomes

Higher scores indicate worse symptoms except for the MIS measure in which higher scores indicate greater marital satisfaction.

Table 5 Predictors of caregivers' outcomes

Table displays output for forward regression analyses except for Marital Intimacy which is a hierarchical regression analysis. Adj., Adjusted; β, standardised beta; ALSFRS–R Limb, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised Limb subscale; FrSBe Tot., Frontal Systems Behaviour Scale Total T score; MIS pre–illness, Marital Intimacy Scale score rated for period two years prior to ALS onset.

Supplementary Appendix

Table S1 Information regarding larger parallel study investigating cognitive-behavioural changes in ALS

Study Aims	i) to delineate the nature and extent of changes in social cognition in ALS and ii) to determine the relationship between such changes and interindividual differences in mood, behaviour, personality, empathy and ALS–related executive dysfunction.				
Sample	55 ALS patients and 49 Healthy Controls				
Control sample demographics (n=49)	**Mean**	**SD**	**Range**	**N**	**%**
Age	60.0	9.7	36-73		
Education (years)	14.5	2.7	10-23		
HADS-R Anxiety[a]	4.4	3.0	0-12		
HADS-R Depression[a]	2.0	2.0	0-7		
Gender Female				15	30.6

[a]Hospital Anxiety and Depression Scale-Revised version (Gibbons et al, 2011)

Gibbons, C., Mills, R., Thornton, E., Ealing, J., Mitchell, J., Shaw, P., Talbot, K., Tennant, A., & Young, C. A. (2011). Rasch analysis of the hospital anxiety and depression scale (hads) for use in motor neurone disease. *Health and Quality of Life Outcomes, 9*(1), 1-8.

Table S2. Correlations between caregiver outcome variables

R **(*p*–values)**	**HADS A**			
HADS A	1.00	**HADS D**		
HADS D	**0.42** **(0.01)**	1.00	**ZBI**	
ZBI	**0.37** **(0.03)**	**0.57** **(<0.001)**	1.00	**MIS** **Current**
MIS **Current**	0.10 (0.63)	-0.06 (0.77)	**-0.45** **(0.009)**	1.00

HADS, Hospital Anxiety and Depression Scale scores (n = 35): A (anxiety subscale), D (depression subscale); ZBI, Zarit Burden Interview (n = 34); MIS, Marital Intimacy Scale (n = 32).

Table S3 Demographic, disease and cognitive profile of 9 ALS patients who spouse declined participation

Measure	Mean	SD	Min-Max	N	Cut-off	No. (%)[a]
Age	57.7	8.2	43-65	9		
Age at symptom onset	54.8	8.2	40-63	9		
Education (years)	14.4	3.6	9-19	9		
Months since symptom onset	35.2	26.9	13-82	9		
Months since diagnosis	16.3	23.9	3-76	9		
ALSFRS-R Total (max 48)	34.2	8.2	22-45	9		
ALSFRS-R Bulbar (max 12)	9.8	1.6	8-12	9		
ALSFRS-R Limb (max 12)	13.3	8.4	0-23	9		
ALSFRS-R Respiratory (max 12)	11.1	0.8	10-12	9		
Epworth Scale (max 24)	4.3	3.3	0-10	9		
HADS-R Depression score	2.2	1.9	0-6	9	8	0 (0)
HADS-R Anxiety score	5.4	2.9	2-10	9	9	2 (22.2)
Executive Function Composite	0.2	0.8	-0.4-2.1	9	1.6	1 (11.1)
Social Cognition Composite	0.7	0.5	-0.8-0.9	9	1.7	0 (0)
VFI – S words	4.7	3.1	1.5-10.8	9	8.6	2 (22.2)
VFI – C words	12.7	10.2	5.6-39.3	9	20.7	0 (0)
DKEFS Card Sorting	5.6	1.7	3-8	9	12	0 (0)
DKEFS Card Sorting Description	21.2	5.9	12-32	9	47	0 (0)
Brixton errors	18.3	6.0	9-29	9	29.5	0 (0)
TASIT Emotion Evaluation Test	5.0	1.4	3-7	9	11	0 (0)
TASIT Social Inference Minimal	8.8	4.4	4-17	9	17	1 (11.1)
TASIT Social Inference Enriched	12.0	5.6	4-22	9	25	0 (0)
Happé Cartoons task 1	10.7	1.7	8-13	7	20.6	0 (0)
Happé Cartoons task 2	10.0	4.9	2-18	7	18.6	0 (0)
Happé Scenarios	9.7	5.2	6-20	6	19.1	1 (16.7)
RME	9.4	3.2	6-15	9	17	0 (0)

Higher scores indicate worse mood, cognitive performance and greater behavioural impairment.
[a]Number and percentage of patients meeting cut-off criteria for 'caseness' (HADS-R), performance at or

below 5th percentile of controls (composites and cognitive tests scores).

Figure 1 Number of impairments on tests of executive function, social cognition and FrSBe domains