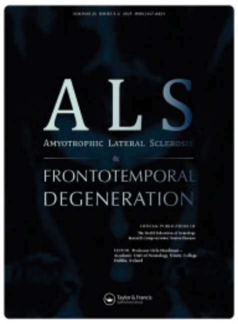

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: www.tandfonline.com/journals/iafd20

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To cite this article: Ratko Radakovic, Debbie Gray, Ana Paula Trucco, Allan Bregola, Eneida Mioshi, Helen Copsey, David Dick, Judith Newton, Shuna Colville, Suvankar Pal, Siddharthan Chandran, Zachary Simmons & Sharon Abrahams (2025) Impact of apathy over the course of disease in amyotrophic lateral sclerosis, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 26:5-6, 516-525, DOI: 10.1080/21678421.2025.2495020

To link to this article: https://doi.org/10.1080/21678421.2025.2495020

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2025; 26: 516–525

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RESEARCH ARTICLE

Impact of apathy over the course of disease in amyotrophic lateral sclerosis

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Abstract

Objective: Apathy is a common syndrome in amyotrophic lateral sclerosis (ALS), particularly Initiation apathy (lack of motivation for self-generated thoughts and/or actions). The aim was to determine how apathy subtypes change over time, and their impact on individuals' quality of life (QoL), caregiver-wellbeing and burden or strain. *Methods*: Forty-nine people living with ALS (pwALS) and their caregiver participated in interviews at three time-points (3-month intervals). They completed the Dimensional Apathy Scale (DAS), and assessments of depression, anxiety and emotional lability, cognitive-behavioral functioning and functional disability. PwALS QoL, caregiver burden or strain, caregiver-wellbeing and care-related QoL were measured. *Results*: At baseline, Initiation apathy was most common (38.8%, $N = 19$) followed by Emotional apathy (16.3%, $N = 8$). Lower caregiver-wellbeing was observed in Initiation apathy ($p < 0.05$) and Mixed-emotional apathy ($p < 0.001$) groups, where only Initiation apathy had higher caregiver burden or strain ($p < 0.05$) than those with no apathy. Over three visits ($N = 31$), there was an increase in Initiation apathy ($p < 0.01$) and Executive apathy ($p < 0.05$) over time. While controlling for functional disability, only increasing Emotional apathy was associated with increasing caregiver burden or strain ($p < 0.05$), decreasing caregiver-wellbeing ($p < 0.001$), and decreasing care-related QoL ($p < 0.05$). *Conclusion*: Initiation and Emotional apathy were variably associated with higher levels of caregiver burden or strain and decreased caregiver-wellbeing in ALS. As ALS progresses, Initiation and Executive apathy increased, while Emotional apathy has been shown to impact care-related QoL, caregiver-wellbeing and burden or strain. This has implications for understanding the progression of apathy subtypes and the interplay of caregiver-wellbeing, QoL, burden, or strain.

Keywords: *Apathy, amyotrophic lateral sclerosis, quality of life, caregiver burden, longitudinal*

Introduction

Amyotrophic lateral sclerosis (ALS) as a progressive, terminal condition, with physical and functional deterioration, is also characterized by cognitive and behavioral impairments (1). Apathy is a behavioral difficulty characterized by a lack of motivation toward goal-directed behaviors (2) and is the most prevalent behavior impairment in

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/21678421.2025.2495020.

(Received 21 January 2025; revised 19 March 2025; accepted 13 April 2025)

ISSN 2167-8421 print/ISSN 2167-9223 online

DOI: 10.1080/21678421.2025.2495020

people living with ALS (pwALS), with prevalence rates of around 50% (1,3).

To date, research specifically examining apathy in relation to wellbeing, quality of life (QoL) and caregiver burden or strain in ALS has been limited. However, behavioral impairment for pwALS has been shown to be associated with higher levels of depression and a lower QoL than those without any behavioral impairment (4). Moreover, behavioral impairment in pwALS, particularly with regards to motivation and apathy, was significantly associated with higher levels of caregiver burden or strain, as well as higher caregiver depression and lower caregiver QoL (5,6). Further research has also shown that apathy in pwALS significantly predicts caregiver burden or strain (7,8). Apathy has been shown to increase through different stages of ALS and apathy has been shown to increase as the disease progressed (9,10). However, a major limitation of these studies is that they measured apathy as a unidimensional construct and did not consider the confounding impact of physical disability, thus limiting the inference of such findings.

It is now widely accepted that apathy is composed of different subtypes and can be subsumed under the Dimensional Apathy Framework (11). This characterizes apathy as a lack of motivation in three main areas: Executive apathy (a lack of motivation toward planning, organization, and attention), Emotional apathy (emotional neutrality/indifference, emotional or affective blunting or flatness), and Initiation apathy (a lack of motivation toward self-generated thoughts, ideas, and/or actions). The Dimensional Apathy Scale (DAS) is used to assess these different apathy subtypes independent of physical disability and has shown a characteristic apathy profile in ALS, whereby Initiation apathy is the most prevalent subtype (3,12). However, the impact of specific apathy subtypes on functioning in everyday life over time has not yet been explored in pwALS and their families.

The aims of this study were to investigate how specific types of apathy change across time and the impact of these subtypes on QoL (both for the caregiver and pwALS) and caregiver burden or strain in ALS.

Methods and materials

Participants

Forty-nine pwALS and their caregivers were recruited via opportunity sampling methods from two sites: the University of Edinburgh, the Scottish MND Register which is part of the Clinical Audit Research Evaluation-MND (CARE-MND) (13) project, and the University of East Anglia, through the Norfolk MND Care and Research Network. All pwALS were diagnosed using the El Escorial Revised Criteria (14). PwALS were excluded if they had a major co-morbid medical, neurological or psychiatric history or had no reliable caregiver or informant.

Ethical approval was obtained from the National Health Service (NHS) South East Scotland Research Ethics Committee 02 and informed consent was obtained from all participants.

Procedure

PwALS and their caregivers took part in interviews at three time points (baseline, 1st follow-up, and 2nd follow-up), at 3-month intervals. At each time point, pwALS completed a series of cognitive measures and questionnaires assessing their own apathy, mood, wellbeing, QoL, cognitive functioning, and functional disability. Additionally, ALS caregivers completed the apathy questionnaire assessing their observation of individuals' apathy, as well as questionnaires assessing their own wellbeing, QoL and burden or strain. ALS caregivers also completed an interview assessing their observation of individuals' behavior change (see below for assessment details).

Assessments

Demographics (age, sex, and education) and clinical (disease duration, site onset, noninvasive ventilation, and gastrostomy use) variables were collected and available.

Apathy, cognitive functioning, behavior, and affect. The self-rated and caregiver-rated DAS (3) are both 24-item measures that assessed multidimensional apathy, completed by pwALS about themselves and by caregivers about their observations of pwALS. The DAS is comprised of three subscales which assess three subtypes of apathy: Executive, Emotional, and Initiation apathy. Total scores for each subscale range from 0 (no apathy) to 24 (high apathy), with a maximum combined total score of 72. The DAS is both a valid and reliable measure of identifying apathy subtypes in ALS, independent of physical disability, with published subtype cutoffs available (3).

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (15) a multi-domain cognitive assessment, completed with pwALS, that assesses functions typically affected in ALS. Total cognitive score can range from 0 (most impaired) to 136 (most intact), with a cut-off of less than or equal to 105 indicative of cognitive impairment. It includes a behavior interview, based on the diagnostic criteria for frontotemporal dementia (FTD), which was also undertaken with a caregiver. The scoring system for the ECAS Behavior interview ranges from 0 to 10 (higher indicative of more behavioral impairment) and the psychosis screen was scored 0–3 (higher scores indicative of more presence of psychotic symptoms). Alternative forms of the ECAS were available and used to mitigate practice effects for longitudinal assessment (16).

The Patient Health Questionnaire (PHQ-9) (17) was used as a nine-item measure of self-rated frequency of depression symptoms, completed by pwALS about themselves. Total scores range from 0 to 27, with higher scores indicating greater depression severity.

The Generalized Anxiety Disorder Scale (GAD-7) (18) was used as a seven-item measure of self-rated frequency of anxiety symptoms, completed by pwALS about themselves. Total scores range from 0 to 21, with higher scores indicating more severe anxiety.

The Emotional Lability Questionnaire (ELQ) (19) is a 33-item questionnaire assessing the incidence and severity of incongruous episodes of: Laughing, Crying, and Smiling. Each subscale has a maximum score of 31 producing a maximum total score of 93, with higher scores indicating higher levels of perceived emotional lability.

Quality of life and burden/strain. The ALS-Specific Quality of Life Instrument-Short Form (ALSQoL-SF) (20) was used as a 20-item measure of QoL in pwALS, with pwALS rating their own self-perception of QoL. The total score is divided by 20, producing an average total score ranging from 0 to 10, with higher scores indicating better QoL.

The Carer Experience Scale (CES) (21) was used as a six-item measure to assess care-related QoL in caregivers, completed by caregivers about themselves. These are converted to index and tariff scores, where the total ranges from 0 to 100 (22). Lower scores indicate worse care-related QoL.

The Zarit Burden Interview-Short Form (ZBI-SF) (23) was used as a 12-item measure to assess caregiver burden or strain in caregivers, completed by caregivers about themselves. Summed scores range from 0 to 48, with higher scores indicating greater feelings of burden or strain.

The ICEpop CAPability Measure for Adults (ICECAP-A) (24) was used as a five-item measure to assess the overall wellbeing of caregivers, completed by caregivers about themselves. These are converted to index and tariff scores, where the total ranges from 0 to 100 (25). Lower scores indicate lower wellbeing.

Disease-related disability. The ALS Functional Rating Scale-Revised (ALSFRS-R) (26) was used as a 12-item measure to assess the extent of physical disability and disease progression in pwALS. Total scores range from 0 (worst functioning) to 48 (normal functioning), with lower scores indicating greater disability.

Statistical analysis

R software (R Foundation for Statistical Computing, Vienna, Austria) (27) was used for analysis. Distribution of data (parametric or non-parametric) was determined using inspection of histograms and Shapiro–Wilk tests.

Published DAS cutoffs (3) were applied to baseline self-ratings and caregiver-ratings to determine the apathy profile of the sample, where if either was above cutoff, apathy was determined as present. Awareness discrepancy scores on DAS subscales were calculated based on the difference between the self-ratings and the caregiver-ratings, with higher scores indicative of lower awareness. Kruskal–Wallis (H) tests and ANOVA tests (with respective follow-up post hoc Tukey's HSD and Dunn's tests multiple comparisons corrected using false discovery rate), as well as Chi-squared tests were used to compare groups based on the most common apathy subtype profiles and those without apathy at baseline, as well as for participants who completed all time point visits and those who dropped out at any point during the study (at visit 1 or 2).

To examine longitudinal change, repeated measures analysis of variance (RM-ANOVA) with post hoc paired t-tests were performed on all variables for participants who had all three visits. Further, Friedman's test with post hoc Wilcoxon's signed-ranks tests was used as a non-parametric equivalent for a RM-ANOVA. Subsequent analysis utilized different linear models with robust standard errors, to explore main and interaction effects relating to visits and different apathy subtypes (Executive, Emotional, Initiation) based on DAS cutoffs, for pwALS and caregiver QoL, wellbeing, burden, or strain outcome variables (ALSsQoL-SF, ICECAP-A, CES, and ZBI-SF), while controlling relevant identified covariates (e.g. functional decline). Standard errors were clustered to account for unexplained variation of the outcome variable within-subject.

Results

Dropout and attrition

Figure 1 shows recruitment and attrition across three time points. The total attrition from baseline to 2nd follow-up was 36.7% ($N = 18$). Supplementary Table 1 shows that there were no significant differences on all variables between the attrition participant group (those who dropped out after visit 1 or 2) and those who participated in follow-up visits (who completed all three time point visits). The attrition group had significantly lower ALSFRS-R scores than the follow-up participant group. Further there was significantly ($U = 393$, $p < .05$) lower awareness (or higher discrepancy score) for Emotional apathy observed for the attrition group

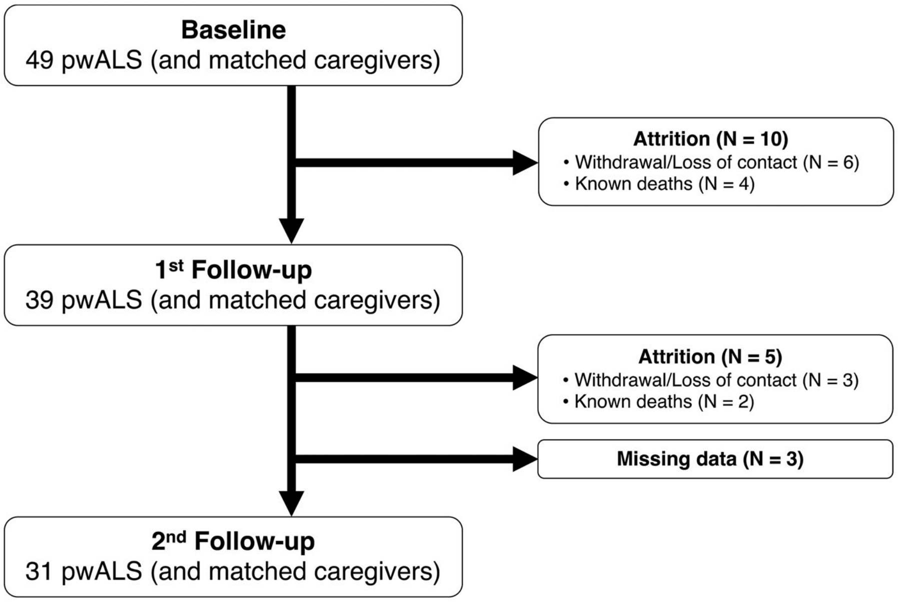

Figure 1. Recruitment flowchart for pwALS and matched caregivers.

($M = 4.3$, SD $= 3.4$) compared to the follow-up participant group ($M = 1.9$, SD $= 1.5$).

Demographics and apathy profile

Table 1 shows descriptive variables of pwALS ($N = 49$) at baseline. The most common relationship of caregivers was a partner or spouse (87.8%, $N = 43$). Based on DAS cutoffs, Initiation apathy was observed in 38.8% ($N = 19$) of pwALS at baseline, followed by Emotional apathy (16.3%, $N = 8$) and finally Executive apathy (10.2%, $N = 5$). A singular Initiation apathy subtype group ($N = 13$) was identified, followed by a Mixed-emotional apathy group ($N = 11$), composed of 72.7% ($N = 8$) Emotional, 54.6% ($N = 6$) Initiation and 45.5% ($N = 5$) Executive apathy. There was also a no apathy group ($N = 25$) identified.

As shown in Table 1, there was a significant difference across groups for caregiver ICECAP-A and ZBI-SF. Only the Initiation apathy group had significantly higher ZBI-SF scores than those with no apathy ($p < .05$), while both Initiation apathy ($p < .05$) and Mixed-emotional apathy ($p < .001$) groups had significantly lower caregiver ICECAP-A scores than those with no apathy. Further, for the Initiation apathy ($p < .05$) and Mixed-emotional apathy ($p < .001$) group, there was a significantly higher ECAS Behavioral scores than the no apathy group, while those Mixed-emotional apathy had significantly worse ECAS Cognitive total scores than those with no apathy ($p < .05$). Additionally, the Initiation apathy group had a significantly higher proportion of noninvasive ventilation ($p < .001$).

In terms of the DAS, the Mixed-emotional apathy group had a significantly higher caregiver-rated DAS scores across all subscale scores than those with no apathy (ps $< .001$). Further, caregiver-rated DAS Emotional apathy scores were significantly higher in the Mixed-emotional apathy group compared to the Initiation apathy group ($p < .001$). Caregiver-rated DAS Initiation apathy scores were significantly higher in both the Initiation apathy and Mixed-emotional apathy group compared to the no apathy group (ps $< .001$), with a similar finding for the caregiver-rated DAS Executive apathy scores (Initiation apathy vs. no apathy group, $p < .01$; Mixed-emotional apathy vs. no apathy group, $p < .001$). For the self-rated DAS, Initiation apathy scores were significantly higher in the Mixed-emotional ($p < .05$) and the Initiation apathy ($p < .001$) groups compared to the no apathy group. There was a significant awareness discrepancy observed for Emotional apathy ($H(2) = 11.61$, $p < 0.01$), with the Mixed-emotional apathy group ($M = 6.6$, SD $= 3.6$) showing significantly lower awareness (or higher discrepancy score) for Emotional apathy compared to the Initiation apathy ($M = 2.2$, SD $= 1.8$) and no apathy ($M = 2.7$, SD $= 2.4$) groups (ps $< .01$).

Apathy subtypes and caregiver wellbeing across time

Of those participants who completed all visits ($N = 31$), there were significant differences across the three time points (see Table 2 for detail).

Figure 2(a) shows the caregiver-rated DAS subscale scores across visits. There was a significant increase in Initiation apathy across visits between visits 2–3 ($p < .05$) and visits 1–3 ($p < .01$) and Executive apathy was also found to significantly increase but only between visits 1 and

Table 1. Baseline demographic, cognitive, behavioral, wellbeing, quality of life, burden and apathy variables of all pwALS and caregivers ($N = 49$).

	All participants (N = 49)	Initiation apathy subgroup (N = 13)	Mixed-emotional apathy subgroup (N = 11)	No apathy subgroup (N = 25)	Statistic ($F/H/\chi^2$)	p Value
Age (mean, SD)	68.0 (7.7)	66.2.9 (7.2)	70.8 (6.9)	67.6 (8.2)	$F = 1.51$	0.325
Gender (M/F)	43/6	13/0	10/1	20/5	$\chi^2 = 3.32$	0.191
Education, years (mean, SD)	11.3 (1.2)	11.0 (1.1)	11.4 (1.5)	11.4 (1.2)	$F = 0.53$	0.573
Disease duration, months (median, IQR)	11 (9)	12 (6)	7 (7)	12 (9)	$H = 2.121$	0.346
Site onset N (L, B, R, M, Unk)	30, 10, 3, 3, 4	7, 4, 1, 1, 0	5, 3, 0, 0, 3	17, 3, 2, 2, 1	$\chi^2 = 11.78$	0.300
ALSFRS-R (mean, SD)	34.6 (7.7)	29.5 (10.2)	36.2 (7.3)	36.6 (5.1)	$H = 4.36$	0.113
Gastrostomy, % (N)	8.2 (4)	15.4 (2)	9.1 (1)	4.0 (1)	$\chi^2 = 1.50$	0.474
NIV, % (N)	28.6 (14)	61.5 (8)	18.9 (2)	16.0 (4)	$\chi^2 = 9.44$	**0.009**
PHQ-9 (mean, SD)	5.6 (4.4)	7.3 (4.4)	5.8 (5.3)	4.6 (3.8)	$H = 3.49$	0.175
GAD-7 (mean, SD)	3.0 (3.7)	4.2 (4.0)	2.9 (4.8)	2.9 (2.9)	$H = 3.53$	0.171
ELQ (mean, SD)	7.3 (11.0)	11.1 (12.3)	2.0 (3.6)	7.6 (11.8)	$H = 4.04$	0.132
ECAS total (mean, SD)	106.9 (13.8)	105.0 (14.1)	99.4 (14.0)	111.2 (12.4)	$H = 6.58$	**0.037**
ECAS impaired % (N)	30.6 (15)	38.5 (5)	54.6 (6)	16.0 (4)	$\chi^2 = 5.74$	0.057
ECAS Behavior (median, IQR)	1 (2)	2 (2)	2 (3.5)	0 (1)	$H = 14.49$	**<0.001**
ECAS Psychosis (median, IQR)	0 (0)	0 (0)	0 (0)	0 (0)	$H = 1.23$	0.540
DAS (caregiver-rated)						
Executive (mean, SD)	6.2 (4.8)	7.8 (3.7)	10.6 (6.0)	3.4 (2.6)	$H = 17.13$	**<0.001**
Emotional (mean, SD)	8.8 (4.3)	8.0 (3.4)	13.4 (4.5)	7.1 (3.1)	$F = 12.53$	**<0.001**
Initiation (mean, SD)	12.1 (5.6)	16.4 (4.8)	15.6 (5.2)	8.6 (3.9)	$F = 15.99$	**<0.001**
DAS (self-rated)						
Executive (mean, SD)	4.6 (4.3)	4.5 (2.8)	6.2 (6.5)	3.9 (3.6)	$H = 0.86$	0.651
Emotional (mean, SD)	9.3 (3.7)	8.8 (2.4)	11.3 (4.9)	8.8 (3.5)	$F = 2.08$	0.137
Initiation (mean, SD)	11.4 (4.7)	14.6 (3.8)	13.4 (4.3)	9.0 (3.9)	$F = 10.05$	**<0.001**
ALSsQoL-SF average item (mean, SD)	6.1 (1.5)	5.6 (1.7)	6.0 (1.2)	6.4 (1.5)	$H = 2.16$	0.340
ICECAP-A (mean, SD)[a]	80.2 (19.2)	68.1 (15.3)	74.6 (26.2)	89.6 (12.4)	$H = 16.74$	**<0.001**
CES (mean, SD)[a]	78.3 (15.1)	73.3 (12.2)	74.5 (20.9)	82.6 (11.4)	$H = 3.96$	0.138
ZBI-SF (mean, SD)[a]	11.3 (9.1)	16.5 (8.1)	13.5 (11.0)	7.7 (7.2)	$H = 9.00$	**0.011**

N: number; M: male; F: female; SD: standard deviation; IQR: interquartile range; L: limb; B: bulbar; R: respiratory; M: mixed; Unk: unknown; ALSFRS-R: ALS Functional Rating Scale-Revised; NIV: noninvasive ventilation; PHQ-9: Patient Health Questionnaire 9; GAD-7: generalized anxiety disorders 7; ELQ: Emotional Lability Questionnaire; ECAS: Edinburgh Cognitive and Behavioural ALS Screen; DAS: Dimensional Apathy Scale; ALSsQoL-SF: ALS Specific Quality of Life-Short Form Instrument; ICACAP-A: ICAcap CAPability measure for adults; CES: Carer Experience Scale; ZBI-SF: Zarit Burden Interview-Short Form.

Additional subgroup comparison of pwALS with Initiation apathy, Mixed-emotional apathy, and No apathy. Statistically significant results in bold.

[a] Caregiver variables.

3 ($p < .05$). Additionally, Table 2 shows that there was a significant decrease in self-rated DAS Emotional apathy scores, only between visits 1 and 3 ($p < .05$). ZBI-SF scores were found to significantly increase across all visits (ps $< .01$). Further Figure 2(b) shows CES scores were also found to significantly decrease across visits, only between visits 1 and 3 ($p < .01$). Additionally, ECAS Behavioral total scores significantly increased across visits, specifically between visits 1–2 ($p < .01$) and visits 1–3 ($p < .05$), and disease duration significantly increased across all visits (ps $< .001$), ALSFRS-R significantly declined across all visits (ps $< .05$). In terms of awareness discrepancy, there was no significant difference for any DAS subscale across visits.

Table 2. Functional, cognitive, behavioral, wellbeing, quality of life, burden and apathy variables across time (baseline, 1st follow-up, and 2nd follow-up) in pwALS and caregivers ($N = 31$).

	Baseline	1st follow-up	2nd follow-up	$F\chi^2/F$ value	*p* Value
Disease duration (median, IQR)	12 (10.0)	15 (11.5)	18 (11.0)	$F = 1235$	**<0.001**
ALSFRS-R (mean, SD)	36.5 (6.9)	35.1 (7.3)	32.0 (8.3)	$F\chi^2 = 21.83$	**<0.001**
Gastrostomy, % (*N*)	3.2 (1)	6.5 (2)	12.9 (4)	$F\chi^2 = 2.8$	0.247
NIV, % (*N*)	19.4 (6)	25.8 (8)	35.5 (11)	$F\chi^2 = 6.33$	**0.042**
PHQ-9 (mean, SD)	5.8 (4.5)	5.5 (3.8)	6.2 (4.3)	$F\chi^2 = 1.12$	0.572
GAD-7 (mean, SD)	3.3 (4.1)	2.5 (2.6)	3.4 (4.0)	$F\chi^2 = 1.52$	0.469
ELQ (mean, SD)	6.8 (11.3)	6.2 (11.2)	8.9 (14.9)	$F\chi^2 = 1.16$	0.561
ECAS Total (mean, SD)	108.4 (12.3)	110.7 (10.5)	108.5 (14.7)	$F\chi^2 = 1.83$	0.400
ECAS (% impaired)	29.0	25.8	35.5	$F\chi^2 = 1.75$	0.417
ECAS Behavior (median, IQR)	1 (2.5)	1 (3.5)	2 (3)	$F\chi^2 = 14.60$	**<0.001**
ECAS Psychosis (median, IQR)	0 (0)	0 (0)	0 (0)	$F\chi^2 = 3.82$	0.148
DAS (caregiver-rated)					
Executive (mean, SD)	6.7 (5.3)	7.3 (5.7)	8.1 (6.2)	$F\chi^2 = 8.39$	**0.015**
Emotional (mean, SD)	9.4 (4.4)	10.3 (4.8)	10.1 (5.0)	$F = 1.03$	0.363
Initiation (mean, SD)	12.3 (5.9)	13.5 (5.4)	14.8 (6.2)	$F\chi^2 = 12.22$	**0.002**
DAS (self-rated)					
Executive (mean, SD)	5.2 (4.3)	4.6 (4.3)	4.7 (3.0)	$F\chi^2 = 1.45$	0.485
Emotional (mean, SD)	9.7 (4.1)	8.9 (3.6)	8.3 (3.8)	$F = 3.46$	**0.038**
Initiation (mean, SD)	12.0 (4.4)	11.7 (4.6)	12.0 (4.3)	$F = 0.12$	0.891
DAS % impaired (*N*)					
Executive	12.9 (4)	16.1 (5)	22.6 (7)	$F\chi^2 = 2.00$	0.368
Emotional	22.6 (7)	25.8 (8)	25.8 (8)	$F\chi^2 = 0.20$	0.905
Initiation	38.7 (12)	48.4 (15)	58.1 (18)	$F\chi^2 = 6.75$	**0.034**
ALSsQoL-SF average item (mean, SD)	6.1 (1.5)	6.2 (1.3)	6.0 (1.5)	$F\chi^2 = 1.38$	0.502
ICECAP-A (mean, SD)a	83.4 (16.9)	77.6 (16.4)	76.0 (19.0)	$F\chi^2 = 3.30$	0.192
CES (mean, SD)[a]	79.2 (13.1)	76.7 (15.2)	71.6 (21.0)	$F\chi^2 = 7.39$	**0.025**
ZBI-SF (mean, SD)[a]	9.6 (7.1)	12.2 (7.2)	15.6 (9.8)	$F\chi^2 = 24.36$	**<0.001**

$F\chi^2$: Friedman's test Chi-squared; *N*: number; M: male; F: female; SD: standard deviation; IQR: interquartile range; L: limb; B: bulbar; R: respiratory; M: mixed; Unk: unknown; ALSFRS-R: ALS Functional Rating Scale-Revised; NIV: noninvasive ventilation; PHQ-9: Patient Health Questionnaire 9; GAD-7: generalized anxiety disorders 7; ELQ: Emotional Lability Questionnaire; ECAS: Edinburgh Cognitive and Behavioural ALS Screen; DAS: Dimensional Apathy Scale; ALSsQoL-SF: ALS Specific Quality of Life-Short Form Instrument; ICACAP-A: ICAcap CAPability measure for adults; CES: Carer Experience Scale; ZBI-SF: Zarit Burden Interview-Short Form.

Statistically significant results in bold.

[a]Caregiver variables.

Impact of apathy subtypes

Table 3 shows exploration of main and interaction effects for visit and different apathy subtypes, with different pwALS QoL (ALSsQoL-SF) and caregiver outcomes (ICECAP-A, CES, ZBI-SF), while controlling for ALSFRS-R score.

There were significant interaction effects between visit and Emotional apathy for all caregiver variables (ICECAP-A, CES, ZBI-SF), indicative of apathy increasing in concordance with decreasing caregiver wellbeing and increasing burden or strain. No such interaction effects were found for Executive and Initiation apathy for all outcome variables. Full statistical results can be found in Supplementary Material 2. There was no change or difference in results when this analysis was adjusted for NIV use across visits.

Discussion

These findings show that types of apathy change over the course of the disease and have impact on the pwALS and their caregivers. Similar to previous research (3,28), Initiation apathy (lack of motivation for self-generation of thought and/or action) was the most common apathy subtype at baseline, both when occurring in isolation or alongside other apathy subtypes (i.e. Executive and Emotional). Further to this, those with Initiation apathy were also found to have higher Executive apathy and Emotional apathy indicating an intricate relationship between subtypes (28). Further, at a cross-sectional level, caregivers of pwALS of those with Initiation apathy experienced higher burden or strain and lower wellbeing. Similar such research has shown that increase in "behavioral" characteristics of apathy (akin to that of Initiation apathy) associates with caregiver burden or strain (29). Additionally, those with predominantly Emotional apathy (with presence of other subtypes) displayed worse caregiver wellbeing, with previous research observing that lower pwALS community-connectedness is associated with "emotional" characteristics of apathy (similar to Emotional apathy) (29). Notably, more recent research has found that a loss of sympathy or empathy as a behavioral impairment or change for

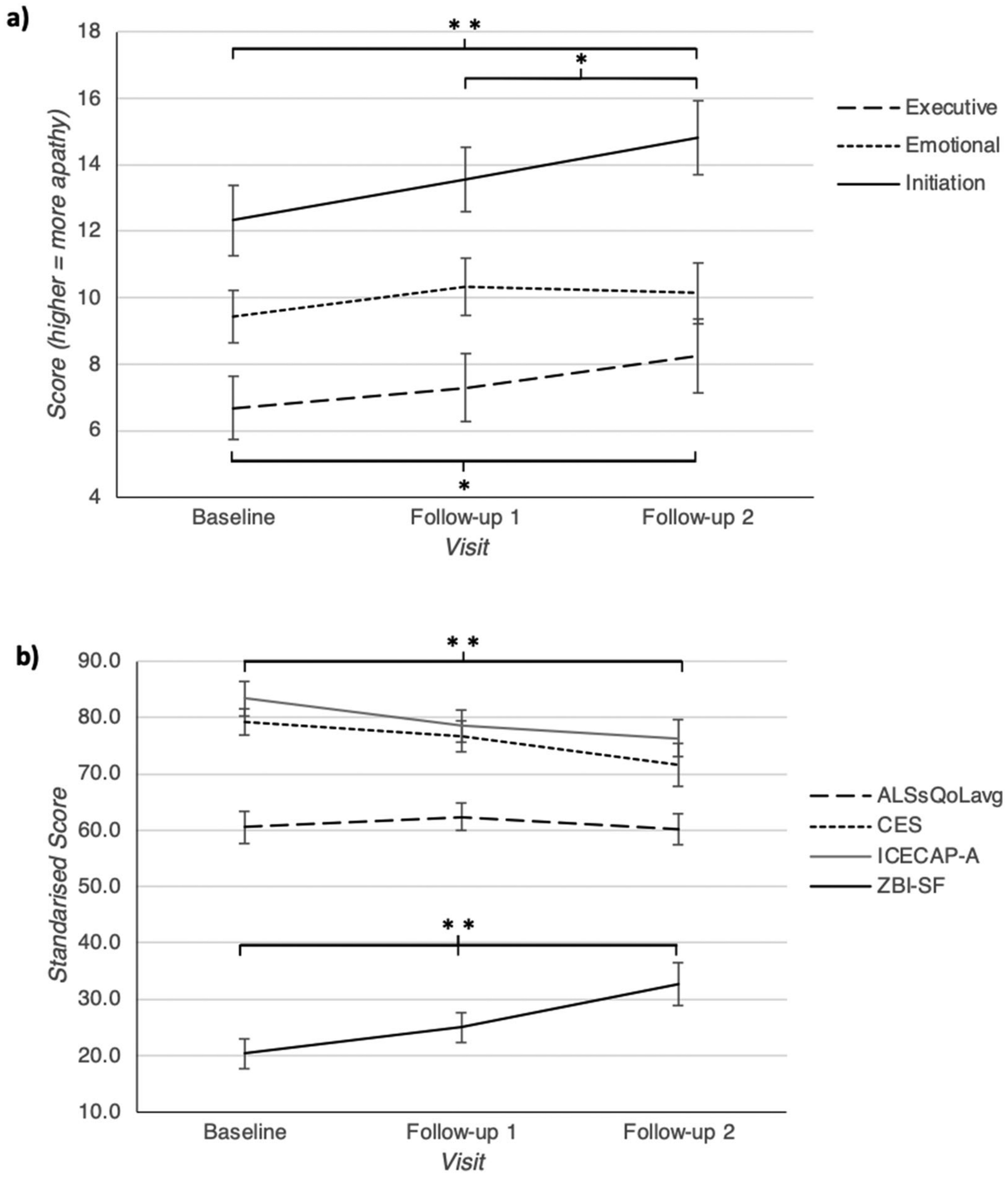

Figure 2. Longitudinal change: (a) apathy subtypes (Executive, Emotional, Initiation across visits and (b) pwALS and caregiver wellbeing (ICECAP-A, CES, ZBI) across visits. DAS: Dimensional Apathy Scale; ALSsQoLavg: ALS Specific Quality of Life-Short Form Average Item Score; ICACAP-A: ICEcap CAPability measure for adults; CES: Carer Experience Scale; ZBI-SF: Zarit Burden Interview-Short Form. (b) Scores were standardized to a 0–100 scale. For the CES, ICACAP-A, and ALSsQoLavg, lower scores indicate lower wellbeing or quality of life. For the ZBI-SF, scores were standardized (0–100) with higher scores indicating higher strain or burden. $^{*}p < 0.05$. $^{**}p < 0.01$.

pwALS (which has similarity to Emotional apathy) can negatively impact pwALS QoL associated with people and the environment (30). This may have an impact on the people supporting pwALS, and account for lower caregiver wellbeing, which may be a systemic area for future research.

When examining change across time, there was a significant increase in Initiation apathy across the three visits indicating an increase as disease progresses. This may be due to the pathological progression of the disease throughout the frontal–subcortical structures, theorized to be associated with motivation (31,32) possibly further compounded by functional decline. While Initiation apathy was associated at baseline with lower caregiver QoL and higher burden or strain, this was not observed across time as the disease progressed in this study. Additionally, self-reported Emotional apathy as found to decrease over time, possibly indicative of more emotional awareness. Speculatively, this may be due to multidisciplinary teams and services in the UK being more attentive to assessment of cognitive and behavioral impairment in recent years (33), which may have led to more support and scaffolding for pwALS and their families, possibly through mechanisms of indirect externalized motivation from healthcare professionals. However, a recent scoping review has found variable, unstandardized guidelines or support strategies for cognitive and/or behavioral difficulties for practitioners and also

Table 3. Summary of linear model results with robust standard errors for different apathy subtypes (Executive, Emotional, Initiation) and outcome variables (ALSsQoL-SF, ICECAP-A, CES, and ZBI-SF).

		Model 1 (outcome ALSsQoL-SF)	Model 2 (outcome ICECAP-A)	Model 3 (outcome CES)	Model 4 (outcome ZBI-SF)
Executive	Main effect visit	No	No	No	**Yes**
	Main effect apathy	No	No	No	No
	Interaction effect visit × apathy	No	No	No	No
Emotional	Main effect visit	No	No	No	No
	Main effect apathy	No	No	No	No
	Interaction effect visit × apathy	No	**Yes**	**Yes**	**Yes**
Initiation	Main effect visit	No	**Yes**	No	**Yes**
	Main effect apathy	No	**Yes**	No	**Yes**
	Interaction effect visit × apathy	No	No	No	No

ALSsQoL-SF: ALS Specific Quality of Life-Short Form Instrument; ICACAP-A: ICAcap CAPability measure for adults; CES: Carer Experience Scale; ZBI-SF: Zarit Burden Interview-Short Form.

Statistically significant results in gray and bold yes. All analysis was controlled for ALSFRS-R. ALSFRS-R was a significant predictor in all models apart from model 3 (outcome CES) Initiation apathy. × signifies interaction effect.

family members in MND (34); therefore, structured exploration of support strategies for specific apathy subtypes may be useful. Furthermore, there is recent research that suggests that Initiation apathy may be related to functional independence for activities of daily living (35), which may have been a mediator and warrant exploration relative to caregiver QoL, wellbeing burden, or strain.

Notably, there were increases in caregiver burden or strain and decline in care-related QoL, across time as the disease progressed, which has been well documented in previous research (5), particularly also associated with apathy (36). In this study, increasing caregiver burden, decline in caregiver wellbeing and care-related QoL were associated with increasing Emotional apathy of pwALS across time, when controlling for functional decline. Previously, apathy has been shown to associate with emotional recognition or social cognition deficits (37), while specifically the Emotional apathy subtype is associated with emotional recognition deficits in ALS (38). Emotional apathy may therefore influence pwALS-caregiver interaction, reciprocal communication and therefore their relationship, which may negatively impact feelings of control and fulfillment relative to care. This might result in reduced engagement of the caregiver relative to support or activities, which may negatively influence their care-related QoL and burden or strain. Recent research has found that behavioral impairments, particularly loss of sympathy or empathy, are associated with pwALS self-perceived QoL to do with interaction with people and environment (30). Loss of sympathy and empathy has characteristic overlap with Emotional apathy (as emotional neutrality/indifference, emotional or affective blunting or flatness), which additionally may account for external, relational and caregiver strain or burden-related difficulties, but further research is needed to elucidate this in the context of QoL. Moreover, Emotional apathy and associated lower awareness toward this subtype have also been shown to be a prominent feature in behavioral variant FTD (39,40), which may be a driver of this negative influence on caregiver variables. This current study found a lower awareness (or higher discrepancy score) for Emotional apathy specifically in the Mixed-emotional apathy group, suggestive of pwALS having lower awareness of motivational difficulties associated with Emotional apathy within this profile group. This might be indicative of subclinical motivational awareness changes that warrant large-scale exploration. Further, while this apathy subtype caregiver burden or strain relationship might require further research, it may be a useful area to explore for future psychological and systemic interventions for both the pwALS and the caregiver.

As with all longitudinal research in ALS, sample size, dropout, and attrition were an issue in this study. Those who dropped out of the study had higher functional disability (as measured by the ALSFRS-R) and lower awareness for their Emotional apathy, which may have created an under-representation of those with more advanced disease who might display behavioral impairment such as apathy. Of note, however, there were no other differences in demographic or clinical variables, notably on apathy subtypes between attrition and follow-up groups in this study. Further comprehensive research is warranted to explore mediators of dropout and attrition (e.g. related to functional disability and awareness of behavioral impairments such as apathy). While a notable strength of the study is that the results are from a generalizable group of pwALS, relative to age range and disease severity or progression, there are limitations in terms of male to female ratio within this study. Future research might benefit from more target recruitment, to explore apathy relating sociodemographic backgrounds, sex, gender, functional disability, and communicative ability of pwALS. Further research should also explore if care packages (inclusive of type of care and how many hours of care caregivers provide) for pwALS may act as a mediator for caregiver wellbeing, burden or strain and implementation of interventions (such as NIV or gastrostomy) in the context of cognitive and behavioral impairment (such as apathy). While the measures of caregiver QoL, wellbeing, and burden have been extensively used in neurodegenerative disease research, it would be useful for future research to utilize (or, if needed, develop) more disease specific measures for further detailed exploration. Due to relatively low group sample size, it was not possible to explore combination apathy subtype deficits and their impact on the minutiae of QoL and caregiver variables, which should be an avenue for future larger cohort research. Furthermore, it might be valuable to explore more long-term trajectories (across 2 years) of apathy subtypes in concordance with changing pwALS and caregiver QoL, to further understand how functional decline impacts this. Finally, more qualitative research may help elucidate perceived experiences of both the pwALS and the caregiver and the impact of cognitive or behavioral impairments such as apathy on functional disability and engagement in activities.

Conclusion

This is the first study to explore how different types of apathy may impact pwALS QoL, that of the caregivers and their burden or strain. Emotional apathy (emotional neutrality/indifference, emotional or affective blunting or flatness) was observed to be related to increasing caregiver burden and decreasing caregiver wellbeing across time. Additionally, Emotional apathy (with presence of other apathy subtypes) and Initiation apathy at a cross-sectional level were associated with lower caregiver wellbeing, while Initiation apathy was also associated with higher caregiver burden or strain but this was not observed across time. This provides foundations for future research to further exploration of the longitudinal course of apathy subtypes in ALS, as well as its consequences in everyday life.

Acknowledgements

Thank you to all the pwALS and their family members or caregivers for taking part in the study. We further appreciate support in data collection from Ms Kaitlin Dudley and the statistical support provided by Dr Stephen Rhodes.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

This study was funded by Motor Neuron Disease Scotland.

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Data availability statement

Data available on request from the authors.

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