



# Prevalence and motor-functional correlates of frontotemporal-*spectrum* disorders in a large cohort of non-demented ALS patients

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## Abstract

**Background** This study aimed at (1) delivering generalizable estimates of the prevalence of frontotemporal-*spectrum* disorders (FTSDs) in non-demented ALS patients and (2) exploring their motor-functional correlates.

**Methods**  $N=808$  ALS patients without FTD were assessed for motor-functional outcomes—*i.e.*, disease duration, severity (ALSFRS-R), progression rate ( $\Delta$ FS), and stage (King's and Milano–Torino—MiToS—systems)—cognition—via the cognitive section of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)—and behaviour—via the ECAS-Carer Interview. Neuropsychological phenotypes were retrieved via Strong's revised *criteria*—*i.e.*, ALS cognitively and behaviourally normal (ALS<sub>cbn</sub>) or cognitively and/or behaviourally impaired (ALS<sub>sci/bi/cbi</sub>).

**Results** Defective ECAS-Total performances were detected in ~29% of patients, with the ECAS-Executive being failed by the highest number of patients (~30%), followed by the ECAS-Language, -Fluency, and -Memory (~15–17%) and -Visuospatial (~8%). Apathy was the most frequent behavioural change (~28%), followed by loss of sympathy/empathy (~13%); remaining symptoms were reported in <4% of patients. The distribution of Strong's classifications was as follows: ALS<sub>cbn</sub>: 46.7%; ALS<sub>sci/bi/cbi</sub>: 22.9%/20.0%/10.4%. Multinomial regressions on Strong's classifications revealed that lower ALSFRS-R scores were associated with a higher probability of ALS<sub>bi</sub> and ALS<sub>cbi</sub> classifications ( $p \leq .008$ ). Higher King's and MiToS stages were associated with a higher probability of ALS<sub>bi</sub> classification ( $p \leq .031$ ).

**Conclusions** FTSDs affect ~50% of non-demented ALS patients, with cognitive deficits being as frequent as behavioural changes. A higher degree of motor-functional involvement is associated with worse behavioural outcomes—with this link being weaker for cognitive deficits.

**Keywords** Amyotrophic lateral sclerosis · Frontotemporal degeneration · Neuropsychology · Epidemiology

## Background

It is thoroughly acknowledged that a non-negligible proportion of non-demented amyotrophic lateral sclerosis (ALS) patients may present with frontotemporal-*spectrum* disorders (FTSDs) [1, 2].

However, currently available prevalence estimates of cognitive (*i.e.*, ~35–50%) [3–5] and behavioural (*i.e.*, ~25–40%) involvement [6, 7] in this population are moderately heterogeneous—possibly as a result of (1) the paucity of large-scale studies and (2) the unsystematic employment of gold-standard, ALS-specific measures of cognition and behaviour

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[8]—such as the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) [9].

In addition, the interplay between motor-functional involvement and FTSDs has been to this day examined on a large scale only within one population-based study [10]—which, however, solely focused on disease staging, and not on other key descriptors (*i.e.*, disease duration, severity and progression rate) [11].

Given the above premises, the current study aimed at (1) delivering generalizable estimates of the prevalence of FTSDs in a large cohort of non-demented ALS patients via a disease-specific screen (*i.e.*, the ECAS) and (2) exploring their motor-functional correlates.

## Methods

### Participants

The present retrospective cohort comprised 901 clinically diagnosed ALS patients without a formal diagnosis of co-morbid frontotemporal dementia (FTD) [12, 13] that were consecutively referred to three Northern Italian centres (*i.e.*, IRCCS Istituto Auxologico Italiano, Milano; Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano; City of Health and Science University Hospital of Turin, Torino) between 2016 and 2023 and for whom both the cognitive section of the ECAS [14] and the ECAS-Carer Interview (ECAS-CI) [15] were available.

Out of the initial pool, 93 patients were excluded as either (1) retrospectively meeting Strong et al.'s [2] neuropsychological criteria for possible behavioural variant-FTD based on both the ECAS and the ECAS-CI (as detailed in Supplementary Table 1)—despite having not received a formal diagnosis of this condition or (2) scoring < 50 on the cognitive section of the ECAS—and thus possibly presenting with a previously undetected dementing condition [16] (Supplementary Fig. 1). The second criterion has been established based on the fact that scores < 50 on the cognitive section of the ECAS have been equated to scores on the Mini-Mental State Examination  $\leq 22$  [16]—the latter being traditionally suggestive of “mild” dementing syndromes [17]. Supplementary Table 2 describes the excluded patient cohort. The definite cohort thus included 808 ALS patients without dementia.

### Materials

The cognitive section of the ECAS (*range* = 0–136) [14] includes five subscales assessing ALS-specific (*range* = 0–100)—*i.e.*, Language (*range* = 0–28), Fluency (*range* = 0–24), and Executive (*range* = 0–48)—and

ALS-Nonspecific domains/functions (*range* = 0–36)—*i.e.*, Memory (*range* = 0–24) and Visuospatial (*range* = 0–12). The ECAS-CI [15] is a 13-item, caregiver-report questionnaire tapping on the following symptom clusters: (1) *Disinhibition*, (2) *Apathy*, (3) *Loss of sympathy/empathy*, (4) *Perseveration*, (5) *Altered eating behaviour*, and (6) *Psychosis* (*range* = 0–13).

Strong et al.'s [2] classifications—*i.e.*, cognitively and behaviourally normal (ALS<sub>cbn</sub>), cognitively impaired (ALS<sub>ci</sub>), behaviourally impaired (ALS<sub>cbi</sub>), and cognitive and behaviourally impaired (ALS<sub>cbi</sub>)—were retrieved based on single subtest-/item-level scores on both the ECAS-Language-/Fluency-/Executive [18] and the ECAS-CI [15] (as detailed in Supplementary Table 3).

Disease severity was assessed via the ALS Functional Rating Scale-Revised (ALSFRS-R) [19] and its progression rate ( $\Delta$ FS) [20]. Disease stages were retrieved according to both King's [21] and Milano–Torino (MiToS) systems [22] based on single item-level ALSFRS-R scores as *per* Balendra et al.'s [23] algorithm.

### Statistics

Prevalence estimates of cognitive deficits were derived by applying age- and education-stratified Italian cutoffs to the raw scores on each measure of the cognitive section of the ECAS (*i.e.*, on both the ECAS-Total and its subtotal-, subscale-, and subtest-level scores) [14, 18], whilst that of behavioural dysfunctions by computing the frequency of individual symptoms and symptom clusters on the ECAS-CI [15].

To test the association between FTSDs on one hand and disease duration, severity, progression rate, and stage on the other, five separate multinomial regressions were run by addressing Strong et al.'s [2] classifications as the outcome (with three contrasts being estimated, *i.e.*, ALS<sub>cbn</sub> vs. ALS<sub>ci</sub>, ALS<sub>cbi</sub> and ALS<sub>cbi</sub>) and, as predictors, (1) disease duration (in months), (2) the ALSFRS-R, (3)  $\Delta$ FS scores as well as both (4) King's and (5) MiToS scores. Age, education and sex were entered as covariates within all these models. Additionally, disease duration was covaried for within the models addressing ALSFRS-R, King's and MiToS scores as predictors.

Analyses were run via IBM® SPSS® Statistics 27 (IBM Corp., 2021) and jamovi 2.3 (the jamovi project, 2022); the significance threshold was set at  $\alpha = 0.05$ . Within multinomial regression models, missing data regarding disease duration, the ALSFRS-R and derived measures (*i.e.*,  $\Delta$ FS, King's and MiToS scores) were excluded pairwise. The sole patient with a MiToS score of 3 was excluded from these analyses too.

## Results

### Prevalence of FTSDs

Table 1 summarises patients' background and clinical features split by Strong et al.'s [2] classifications, including the proportion of defective performances on the cognitive section of the ECAS and that of positive symptoms/symptom clusters as yielded by the ECAS-CI. Figures 1 and 2 graphically display the proportion of abnormal ECAS and ECAS-CI findings within the whole cohort, respectively, whilst Fig. 3 displays the distribution of Strong's classifications.

Approximately 29% of patients performed defectively on the ECAS-Total, with a similar proportion (~30%) reporting a below-cutoff performance on its ALS-specific subtotal; by contrast, defective scores on the ECAS-ALS-Nonspecific were less frequent (~18%). As to subscale-level measures, the ECAS-Executive was failed by the highest number of patients (~30%), followed by the ECAS-Language, -Fluency, and -Memory (~15–17%). At variance, less than 8% of patients performed defectively on the ECAS-Visuospatial. When looking at subtest-level scores, the highest proportion of defective performances were detected on the *Alternation* (~30%), *Sentence completion* (~22%), and *Retention score* subtests (~19%), followed by those enclosed within the ECAS-Fluency (~16–17%).

In respect to the ECAS-CI, apathy was by far the most frequently caregiver-reported behavioural change (~28%), followed by loss of sympathy/empathy (~13%); remaining symptom/symptom clusters were reported in less than ~4% of patients.

As to Strong's phenotypes, less than 47% of patients were deemed as free of clinically significant both cognitive and behavioural dysfunctions, with remaining ones being classified as ALS*Sci* (~23%), ALS*Sbi* (20%), or ALS*Scbi* (~10%). Interestingly, as shown in Table 1, a small proportion of patients classified as "free" of cognitive impairment according to Strong's *criteria* (*i.e.*, ALS*Scbn* and ALS*Sbi*) still presented with defective scores on both the ECAS-Total and its subtotals, subscales, and subtests, and, conversely, those allotted within ALS*Scbn* and ALS*Sci* categories, despite being supposed to be devoid of behavioural changes, at times presented with positive items on the ECAS-CI.

### Motor-functional correlates of FTSDs

Table 2 shows the results of multinomial regression models on Strong's classifications. The sole motor-functional

predictor yielding significance was the ALSFRS-R ( $\chi^2(3) = 11.80$ ;  $p = 0.008$ ), with the probability of patients being classified as both ALS*Sbi* and ALS*Scbi* (*vs.* ALS*Scbn*) increasing as ALSFRS-R scores decreased (Fig. 4). No *omnibus* effects were detected as to disease duration ( $\chi^2(3) = 1.11$ ;  $p = 0.774$ ),  $\Delta$ FS scores ( $\chi^2(3) = 4.17$ ;  $p = 0.243$ ), and either King's ( $\chi^2(3) = 6.65$ ;  $p = 0.084$ ) or MiToS ( $\chi^2(2) = 6.19$ ;  $p = 0.103$ ) scores. However, when looking at individual contrasts for King's and MiToS scores (Table 2), the probability of patients being classified as ALS*Sbi* (*vs.* ALS*Scbn*) proved to be higher with more advanced stages as *per* both systems (Fig. 5).

## Discussion

This report provides practitioners and researchers with insights into the prevalence and motor-functional correlates of FTSDs in ALS from a large cohort of non-demented patients evaluated over a 7-year timespan by means of a disease-specific screen—*i.e.*, the ECAS. To the best of the authors' knowledge, this study includes the largest-sized cohort of non-demented ALS patients assessed via the ECAS amongst previously published reports—this granting a sufficient degree of generalizability to the present findings [1].

### Prevalence of FTSDs

This study suggests that the proportion of non-demented ALS patients presenting with cognitive impairment (~30% and ~33% if looking at either the ECAS-Total or at the combination of ALS*Sci* and ALS*Scbi* patients, respectively) is much closer to the "lower bound" [1] of the commonly accepted "35-to-50%" range—rather than to its "upper bound" [1–5].

As to patients' cognitive profile, whilst supporting the notion of executive dysfunctions being by far the most represented (~28%) [1], this report also suggests that memory impairment, once deemed as atypical of ALS [24], might be detected almost as often as language and verbal fluency deficits are (15% *vs.* ~18% and ~17%, respectively). In this respect, it is noteworthy that the *Retention* subtest—assessing episodic long-term memory—was the one failed by the highest number of patients (~18%) after those enclosed within the ECAS-Executive. Overall, besides confirming that non-demented ALS patients' cognitive profile mimics that of FTDs [1], these findings also support the increasing amount of evidence hinting at a non-negligible role for memory impairment in this population [24].

Caregiver-rated behavioural changes were herewith found to be as common as abnormal cognitive performances—with the cumulative prevalence of patients being classified

**Table 1** Participants' background and clinical measures

	Total	ALScbn	ALSci	ALSbi	ALScbi
<i>N</i>	808	377	185	162	84
Age (years)	63.1 ± 11 (20–88)	61.0 ± 10.9 (30–88)	67.4 ± 10.1 (29–85)	60.9 ± 11.1 (20–81)	67.2 ± 9.5 (35–84)
Sex (male/female)	55.4%/44.6%	50.9%/49.1%	56.2%/43.8%	60.5%/39.5%	64.3%/35.7%
Education (years)	11.6 ± 4.2 (3–25)	12.2 ± 3.8 (3–25)	10.1 ± 4.7 (3–23)	12.6 ± 3.6 (5–23)	10.3 ± 4.8 (5–24)
Disease duration (months) <sup>a</sup>	19.3 ± 19.5 (1–264)	19.3 ± 22 (1–264)	20.2 ± 17.0 (1–102)	18.2 ± 15.5 (1–108)	20.0 ± 19.1 (2–108)
ALSFRS-R <sup>b</sup>	38.9 ± 5.8 (12–47)	39.7 ± 5.6 (12–47)	38.7 ± 5.6 (23–47)	38.3 ± 6 (20–47)	36.9 ± 6.1 (17–46)
ΔFS <sup>c</sup>	0.8 ± 0.8 (0–7)	0.7 ± 0.9 (0–7)	0.8 ± 0.7 (0–3.5)	0.9 ± 0.8 (0–5)	1.0 ± 0.9 (0.1–4.5)
King's (Stage 1/2/3/4) <sup>c</sup>	38.7%/33.2%/23.7%/4.4%	43.1%/33.6%/20.1%/3.2%	32.7%/38.2%/26.1%/3.0%	36.6%/31.4%/26.1%/5.9%	35.5%/23.7%/30.3%/10.5%
MiToS (Stage 0/1/2/3) <sup>d</sup>	79.2%/18.7%/1.9%/0.1%	82.8%/15.8%/1.4%	79.4%/18.8%/1.8%	75.8%/21.6%/2.6%	70.7%/26.7%/2.7%
Genetics ( <i>N</i> ) <sup>e</sup>					
<i>C9orf72</i>	51	29	10	9	3
<i>SOD1</i>	24	11	2	7	4
<i>TARDBP</i>	20	11	5	3	1
<i>FUS</i>	3	1	0	2	0
<i>OPTN</i>	3	1	2	0	0
<i>SQSTM1</i>	3	3	0	0	0
Other	8	3	1	3	1
ECAS [impaired %]					
Total	100.9 ± 16.5 (50–133) [29.3%]	109 ± 10.5 (68–133) [7.7%]	85.6 ± 15.9 (51–117) [70.8%]	108.2 ± 9.9 (70–129) [8.6%]	84.8 ± 14.8 (50–115) [75.0%]
ALS-Specific	74.2 ± 13.6 (24–98) [29.7%]	81.0 ± 8.4 (49–98) [8.2%]	61.1 ± 12.7 (31–86) [70.8%]	80.7 ± 7.5 (57–97) [5.6%]	59.9 ± 12.0 (24–85) [82.1%]
ALS-Nonspecific	26.8 ± 4.6 (7–36) [17.5%]	28.0 ± 3.9 (14–36) [10.9%]	24.5 ± 5.0 (7–35) [28.6%]	27.5 ± 4.0 (13–34) [14.2%]	24.8 ± 5.1 (11–32) [28.6%]
Language	23.9 ± 3.5 (9–28) [17.8%]	25.1 ± 2.5 (17–28) [6.6%]	21.5 ± 4.1 (9–28) [41.1%]	25.1 ± 2.5 (18–28) [6.8%]	21.6 ± 3.8 (10–28) [38.1%]
Naming	6.8 ± 1.3 (1–8) [12.6%]	7.2 ± 1.0 (4–8) [7.2%]	6.2 ± 1.4 (1–8) [23.8%]	7.2 ± 1.0 (4–8) [4.9%]	6.0 ± 1.4 (2–8) [27.4%]
Comprehension	7.7 ± 0.6 (4–8) [8.0%]	7.8 ± 0.4 (6–8) [2.7%]	7.5 ± 0.8 (4–8) [16.8%]	7.8 ± 0.5 (6–8) [4.3%]	7.3 ± 0.8 (5–8) [20.2%]
Spelling	9.4 ± 2.7 (0–12) [14.2%]	10.1 ± 2.0 (1–12) [6.1%]	7.8 ± 3.4 (0–12) [31.9%]	10.1 ± 2.0 (3–12) [5.6%]	8.3 ± 2.6 (0–12) [28.6%]
Fluency	17.1 ± 5.3 (0–24) [17.1%]	19.7 ± 2.4 (12–24) [1.1%]	12.1 ± 5.6 (0–24) [46.5%]	19.6 ± 2.2 (14–24) [0.0%]	11.3 ± 5.6 (0–22) [57.1%]
Verbal fluency—S	8.8 ± 2.7 (0–12) [16.7%]	9.9 ± 1.3 (6–12) [0.0%]	6.7 ± 3.3 (0–12) [47.6%]	9.9 ± 1.3 (6–12) [0.0%]	5.9 ± 3.5 (0–12) [56.0%]
Verbal fluency—C	8.3 ± 3.3 (0–12) [16.1%]	9.8 ± 1.5 (6–12) [0.0%]	5.4 ± 3.9 (0–12) [49.2%]	9.6 ± 1.5 (6–12) [0.0%]	5.4 ± 3.8 (0–12) [46.4%]
Executive	33.2 ± 7.7 (7–48) [27.5%]	36.2 ± 5.9 (16–48) [13.3%]	27.6 ± 7.9 (11–42) [57.8%]	36.1 ± 5.1 (22–46) [11.1%]	27.1 ± 7.6 (7–44) [56.0%]
Backward digit span	5.4 ± 1.8 (0–12) [1.1%]	5.7 ± 1.8 (2–12) [0.3%]	4.6 ± 1.7 (0–10) [3.8%]	5.9 ± 1.8 (1–12) [0.6%]	4.6 ± 1.5 (2–8) [0.0%]
Alternation	8.9 ± 4.1 (0–12) [29.5%]	9.8 ± 3.6 (0–12) [21.5%]	7.0 ± 4.4 (0–12) [49.7%]	10.1 ± 3.2 (1–12) [16.7%]	7.3 ± 4.4 (0–12) [45.2%]
Sentence completion	9.2 ± 2.4 (0–12) [22.0%]	9.9 ± 1.8 (0–12) [10.3%]	7.7 ± 2.7 (0–12) [44.9%]	9.8 ± 1.8 (1–12) [12.3%]	7.6 ± 2.8 (0–12) [42.9%]
Social cognition	9.8 ± 3.1 (0–12) [10.1%]	10.8 ± 2.5 (0–12) [4.2%]	8.3 ± 3.4 (0–12) [20.0%]	10.3 ± 2.4 (2–12) [4.3%]	7.5 ± 3.7 (0–12) [26.2%]
Memory	15.4 ± 4.1 (0–24) [15.0%]	16.5 ± 3.6 (2–24) [9.3%]	13.6 ± 4.3 (0–23) [27.0%]	16.0 ± 3.7 (2–22) [10.5%]	13.6 ± 4.6 (1–20) [22.6%]
Immediate recall	5.2 ± 1.9 (0–10) [5.6%]	5.7 ± 1.8 (0–10) [3.2%]	4.4 ± 1.9 (0–10) [8.6%]	5.5 ± 1.7 (1–9) [3.7%]	4.3 ± 1.8 (0–8) [13.1%]
Retention score	7.9 ± 2.5 (0–10) [19.2%]	8.3 ± 2 (0–10) [13.8%]	7.2 ± 3.0 (0–10) [29.2%]	8.1 ± 2.3 (0–10) [17.3%]	7.5 ± 3.0 (0–10) [25.0%]
Recognition	2.3 ± 1.2 (0–4) [11.4%]	2.5 ± 1.2 (0–4) [8.8%]	2.0 ± 1.2 (0–4) [14.1%]	2.3 ± 1.2 (0–4) [9.3%]	1.8 ± 1.3 (0–4) [21.4%]
Visuospatial	11.4 ± 1.1 (4–12) [7.8%]	11.5 ± 0.9 (7–12) [5.0%]	10.9 ± 1.4 (4–12) [15.1%]	11.5 ± 0.9 (7–12) [5.6%]	11.3 ± 1.1 (6–12) [8.3%]
Number position	3.9 ± 0.5 (0–4) [10.0%]	3.9 ± 0.3 (1–4) [5.6%]	3.7 ± 0.8 (0–4) [22.7%]	3.9 ± 0.3 (2–4) [6.8%]	3.9 ± 0.5 (0–4) [8.3%]
Dot-counting	3.9 ± 0.4 (1–4) [1.1%]	3.9 ± 0.3 (1–4) [0.8%]	3.8 ± 0.4 (2–4) [2.7%]	3.9 ± 0.3 (3–4) [0.0%]	3.9 ± 0.4 (2–4) [1.2%]
Cube-counting	3.6 ± 0.8 (0–4) [5.1%]	3.7 ± 0.7 (0–4) [4.0%]	3.4 ± 0.9 (1–4) [8.6%]	3.7 ± 0.7 (0–4) [4.3%]	3.5 ± 0.8 (1–4) [3.6%]
ECAS-CI					
Total	0.6 ± 0.9 (0–4)	0.2 ± 0.4 (0–2)	0.2 ± 0.6 (0–2)	1.6 ± 0.7 (1–4)	1.6 ± 0.6 (1–3)
Disinhibition	3.6%	1.9%	3.2%	6.2%	7.1%
Socially inappropriate behaviour	1.2%	1.3%	1.1%	1.9%	0.0%
Loss of manners/decorum	1.5%	0.5%	0.0%	3.7%	4.8%
Impulsiveness	1.6%	0.3%	2.2%	3.1%	3.6%

**Table 1** (continued)

	Total	ALScbn	ALSci	ALSbi	ALSbi
Loss of sympathy/empathy	13.4%	3.4%	4.9%	33.3%	38.1%
Diminished response to others' needs/feelings	5.9%	1.9%	2.7%	16.0%	11.9%
Diminished social interest	9.5%	1.6%	2.7%	24.1%	32.1%
Apathy	28.2%	0.0%	0.0%	90.7%	96.4%
Perseveration	4.2%	2.4%	4.9%	8.0%	3.6%
Simple repetitive movements	3.5%	2.4%	4.3%	6.8%	0.0%
Complex/compulsive/ritualistic behaviour	3.2%	1.3%	4.3%	6.2%	3.6%
Altered eating behaviour	4.2%	4.0%	3.8%	6.2%	2.4%
Altered food preferences	2.7%	2.1%	2.7%	4.9%	1.2%
Binge eating/hyperorality	2.6%	2.7%	3.2%	1.9%	2.4%
Psychosis	1.2%	1.9%	0.5%	1.2%	0.0%
Suspicion	0.6%	0.8%	0.5%	0.6%	0.0%
Delusions	0.4%	0.8%	0.0%	0.0%	0.0%
Hallucinations	0.4%	0.5%	0.0%	0.6%	0.0%

*ALSFRS-R* Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised,  $\Delta$ *FS* progression rate, *ECAS* Edinburgh Cognitive and Behavioural ALS Screen, *MiToS* Milano–Torino staging system, *ECAS-CI* ECAS–Carer Interview, *ALS* amyotrophic lateral sclerosis, *cbn* cognitively and behaviourally normal, *ci* cognitively impaired, *bi* behaviourally impaired, *cbi* cognitively and behaviourally impaired

<sup>a</sup>data available for  $N=775$  patients out of the whole sample (and, more specifically, for  $N=364$  ALScbn,  $N=176$  ALSci,  $N=155$  ALSbi patients and  $N=80$  ALSbi)

<sup>b</sup>data available for  $N=742$  patients out of the whole cohort (and, more specifically, for  $N=348$  ALScbn,  $N=165$  ALSci,  $N=153$  ALSbi patients and  $N=76$  ALSbi)

<sup>c</sup>data available for  $N=742$  patients out of the whole cohort (and, more specifically, for  $N=348$  ALScbn,  $N=165$  ALSci,  $N=153$  ALSbi patients and  $N=76$  ALSbi)

<sup>d</sup> data available for  $N=741$  patients out of the whole cohort (and, more specifically, for  $N=348$  ALScbn,  $N=165$  ALSci,  $N=153$  ALSbi patients and  $N=75$  ALSbi)

<sup>e</sup>data available for  $N=633$  out of the whole cohort (and, more specifically, for  $N=309$  ALScbn,  $N=136$  ALSci and  $N=60$  ALSbi patients)

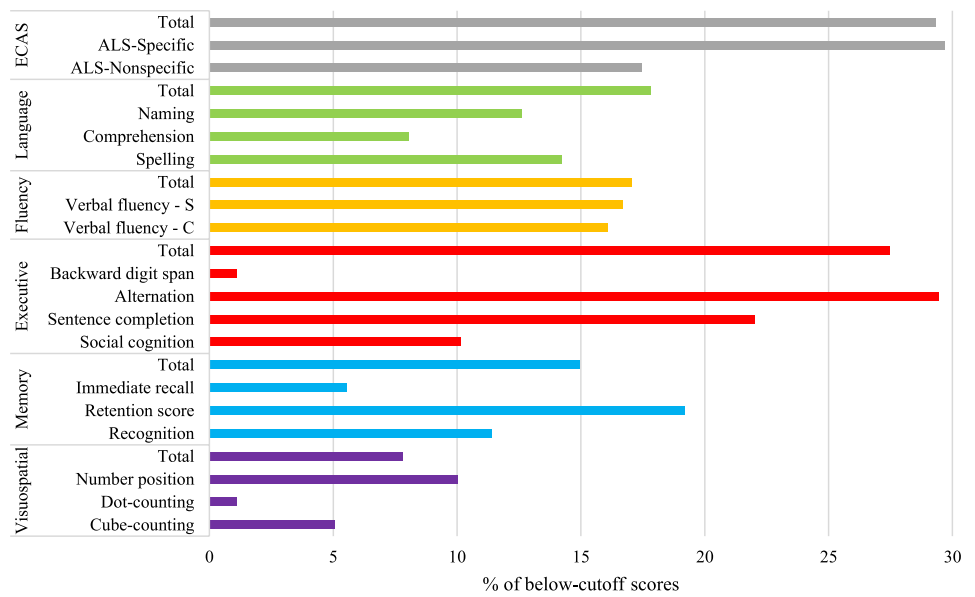
as either ALSbi or ALSbi being ~30%. In alignment with the current knowledge [1], apathy was the most frequently reported change (~28%)—with this estimate closely resembling that resulted from a recent meta-analysis on the topic (~25%) [7]—followed, albeit to a much lower degree, by loss of sympathy/empathy (~13%); at variance, remaining symptom clusters were considerably underrepresented (<5%). Interestingly, such a pattern of behavioural dysfunction happens to be consistent with the previous reports likewise employing the ECAS-CI [25, 26]. These findings thus suggest that behavioural dysfunctions are not less frequent than cognitive deficits in non-demented ALS patients—being mostly driven by apathetic features and, to a lesser extent, by changes in social interactions.

Interestingly, whilst the proportion of patients presenting with either cognitive or behavioural dysfunctions alone

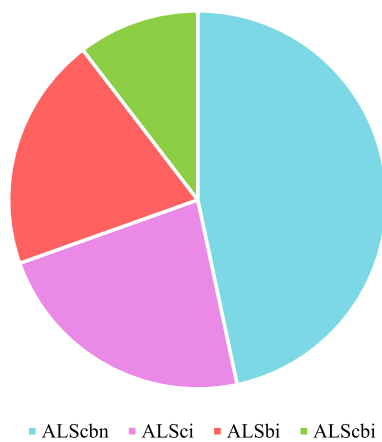
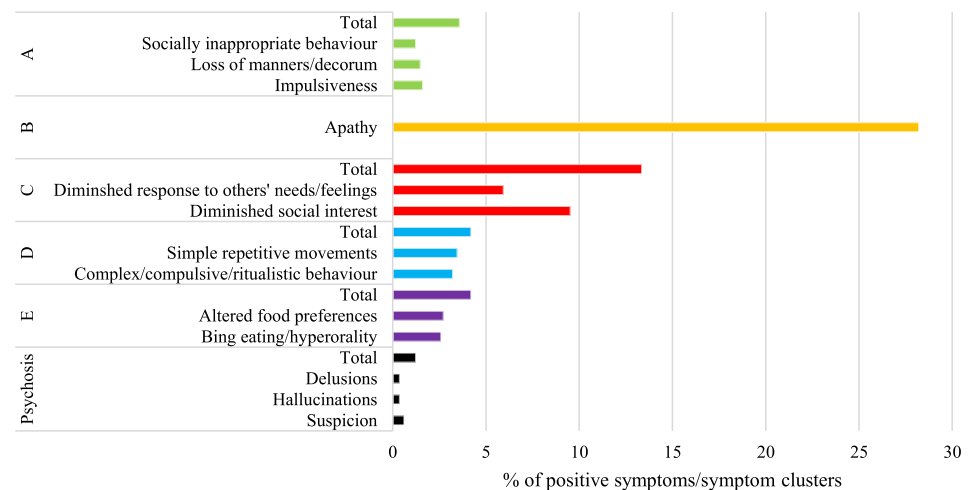
did not exceed ~30%, less than half of the sample (~47%) was classified as free of FTSDs. The latter proportion substantially overlaps with the one reported in a previous, population-based study ( $N=797$ ) [10]—which, however, also included a considerable amount of patients (20.5%) with co-morbid FTD and did not employ the ECAS to assess cognition and behaviour. It might be thus hypothesised that, when synoptically looking at both cognitive and behavioural dysfunctions, the proportion of non-demented ALS patients presenting with FTSDs, if assessed with disease-specific instruments, might be higher than expected. This highlights the need for concurrently assessing both cognition and behaviour to effectively detect extra-motor, frontotemporal involvement in this population.

Furthermore, in this respect, it has to be noted that some patients classified as free of either cognitive (*i.e.*, ALScbn

**Fig. 1** Prevalence of below-cutoff scores on the cognitive section of the ECAS. *ECAS* Edinburgh Cognitive and Behavioural ALS Screen



**Fig. 2** Prevalence of individual symptoms and symptom clusters on from the ECAS-CI. *ECAS-CI* Edinburgh Cognitive and Behavioural ALS Screen-Carer Interview. Letters from A to E denote individual symptom clusters as listed within the ECAS-CI record-form (*i.e.*, *Disinhibition*, *Apathy*, *Loss of sympathy/empathy*, *Perseveration*, and *Altered eating behaviour*, respectively)



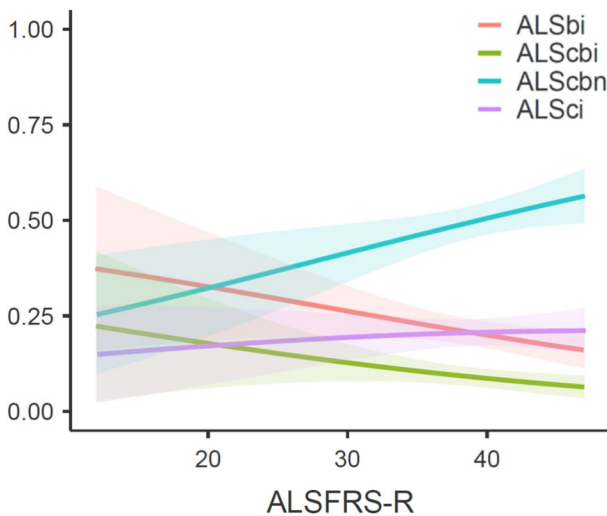
**Fig. 3** Distribution of Strong's classifications. *ALS* amyotrophic lateral sclerosis, *cbn* cognitively and behaviourally normal, *ci* cognitively impaired, *bi* behaviourally impaired, *cbi* cog

and ALSbi) or behavioural (*i.e.*, ALScbn and ALSci) dysfunctions according to Strong's *criteria* presented, albeit infrequently, with defective scores on the cognitive section of the ECAS and positive ECAS-CI items, respectively. On one hand, these findings suggest that a small proportion of patients without clinically significant FTSDs might still present with circumscribed, and possibly subclinical, changes in cognition and/or behaviour. On the other, it might be also hypothesised that Strong's *criteria*, albeit largely comprehensive, are not able to fully capture the *spectrum* of neuropsychological dysfunction in ALS [1]. Such a hypothesis most likely applies to those patients presenting with cognitive deficits outside the executive and language domains—such as memory dysfunctions [24].

**Table 2** Results of multinomial regressions testing the association between motor-functional outcomes and FTSDs

Model	Predictor	Contrast	OR (CI 95%)	z	p
1	Disease duration	ALScbn vs. ALSci	1.00 [0.99, 1.02]	0.61	0.539
		ALScbn vs. ALSbi	1.00 [0.99, 1.01]	− 0.56	0.573
		ALScbn vs. ALScbi	1.00 [0.99, 1.01]	0.41	0.680
2*	ALSFRS-R	ALScbn vs. ALSci	0.99 [0.90, 0.98]	− 0.71	0.476
		ALScbn vs. ALSbi	0.95 [0.95, 1.02]	− 2.73	<b>0.006</b>
		ALScbn vs. ALScbi	0.94 [0.92, 0.99]	− 2.70	<b>0.007</b>
3	$\Delta$ FS	ALScbn vs. ALSci	0.95 [0.91, 1.57]	− 0.37	0.710
		ALScbn vs. ALSbi	1.19 [0.74, 1.23]	1.49	0.136
		ALScbn vs. ALScbi	1.19 [0.95, 1.48]	1.26	0.209
4*	King's	ALScbn vs. ALSci	1.14 [0.99, 1.75]	1.18	0.239
		ALScbn vs. ALSbi	1.28 [0.92, 1.43]	2.15	<b>0.031</b>
		ALScbn vs. ALScbi	1.32 [1.02, 1.59]	1.90	0.057
5*	MiToS	ALScbn vs. ALSci	1.01 [0.93, 2.65]	.40	0.688
		ALScbn vs. ALSbi	1.59 [0.70, 1.71]	2.17	<b>0.030</b>
		ALScbn vs. ALScbi	1.57 [1.05, 2.41]	1.67	0.094

FTSDs frontotemporal-spectrum disorders, ALSFRS-R Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised,  $\Delta$ FS progression rate, MiToS Milano–Torino staging system, ALS amyotrophic lateral sclerosis, *cbn* cognitively and behaviourally normal, *ci* cognitively impaired, *bi* behaviourally impaired, *cbi* cognitively and behaviourally impaired. Age, education, and sex were entered as covariates within each of these model. \*model encompassing disease duration (in months) as a further covariate. Significant *p*-values are in bold



**Fig. 4** Probability of Strong et al.'s [2] classification (y-axis) as a function of ALSFRS-R scores. ALSFRS-R Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised, ALS amyotrophic lateral sclerosis, *cbn* cognitively and behaviourally normal, *ci* cognitively impaired, *bi* behaviourally impaired, *cbi* cognitively and behaviourally impaired. Regression slopes are displayed along with respective 95% CIs

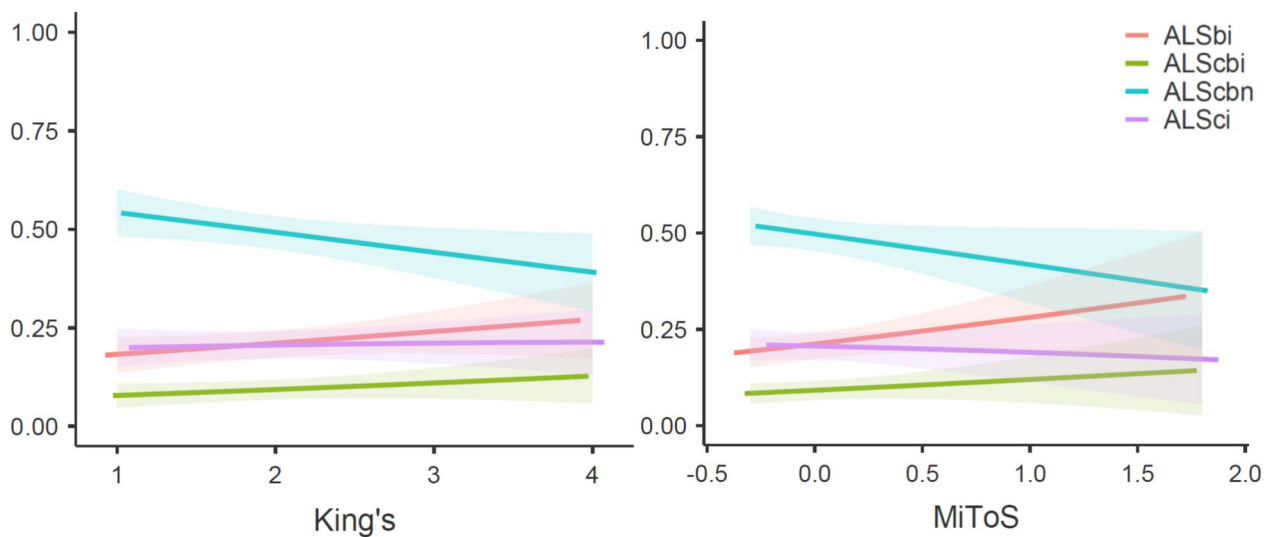
### Motor-functional correlates of FTSDs

Lower ALSFRS-R scores have been herewith found to be associated with a higher probability of both behavioural (*i.e.*, ALSbi) and cognitive *plus* behavioural (*i.e.*, ALScbi)

dysfunctions—whilst not with that of cognitive deficits alone (*i.e.*, ALSci). These findings add up and complement previous investigations linking lower ALSFRS-R scores to worse cognitive and/or behavioural outcomes [27–31] in this population, by clarifying that such an association might selectively apply whenever behaviour is affected—regardless of whether cognition is involved or not.

Interestingly, the results concerning King's and MiToS scores herewith pointed to a similar direction—as more advanced disease stages were found to be associated with a higher probability of behavioural dysfunction (*i.e.*, ALSbi). This finding overall aligns with the previous investigations reporting an increased rate of FTSDs with advancing disease [10, 25]—by nonetheless suggesting that such an occurrence might be restricted to behavioural, and not cognitive, dysfunctions.

By contrast, disease duration and progression rate did not herewith prove to be associated with FTSDs. Whilst the result on disease duration aligns with previous meta-analytic evidence [3], the fact that progression rate was unrelated to FTSDs in the present cohort is not trivial to be framed within the existing literature. Indeed, despite having been reported that a faster decline in motor functions is linked to cognitive/behavioural involvement regardless of its severity [27], it has been also pointed out that this might apply solely to patients with co-morbid FTD, and not to non-demented ones being classified as ALSci/bi/cbi [32]. Additionally, a previous study linking a faster disease to a greater neuropsychological involvement did not employ cognitive/behavioural



**Fig. 5** Probability of Strong's classification (y-axis) as a function of King's (left panel) and MiToS (right panel) scores. *MiToS* Milano-Torino staging system, *ALS* amyotrophic lateral sclerosis, *cbn* cog-

nitively and behaviourally normal, *ci* cognitively impaired, *bi* behaviourally impaired, *cbi* cognitively and behaviourally impaired

measures that compensate for motor disabilities [27]—this potentially accounting for the present, contrasting results.

Taken together, the above-mentioned findings suggest that, in this population, disease severity is linked to changes in behaviour—both when presenting alone and along with cognitive deficits—as well as that the frequency of behavioural dysfunction increases with advancing disease stages.

### Limitations and future perspectives

This study is of course not devoid of limitations.

First, cognition and behaviour have been herewith assessed by means of a screening instrument (*i.e.*, the ECAS)—which, despite having been specifically designed for ALS patients [9] and having shown optimal clinimetric properties [14, 15, 18, 33–35], is not as comprehensive as a full neuropsychological battery. However, in this respect, it should be noted that the prevalence estimates of FTSDs herewith yielded are fairly consistent with those reported within a previous, large-scaled study employing domain-/function-specific cognitive tests and second-level behavioural questionnaires [10]. Moreover, one has to bear in mind that no second-level cognitive battery is currently available that compensates for motor disabilities as the ECAS does.

In this respect, and with specific regard to the cognitive section of the ECAS, it should be also borne in mind that, as previously suggested [36], the proportion of defective performances might vary as a function of the statistical approach employed to derive its norms—with some norming frameworks possibly overestimating, and some others

underestimating, the prevalence of cognitive deficits. For instance, such a methodological issue might have accounted for the unexpectedly low proportion of patients failing the *Backward digit span* of the ECAS-Executive—this having been also reported within the study delivering 2 *SD*-based, subtest-level cutoffs for the Italian ECAS [18]. Replication studies are thus advisable that address a norm-derivation method different from that herewith referred to (*i.e.*, the 2 *SD*-based one).

A related issue lies in the fact that, as previously mentioned, a small proportion of patients being classified as free of cognitive and/or behavioural changes according to Strong's *criteria* still reported abnormal scores on the cognitive section of the ECAS and/or the ECAS-CI. Whilst this occurrence likely affected to a minimal extent the present findings, it raises the need for future investigations aimed at comparing different operationalizations of Strong's *criteria* based on the ECAS—*e.g.*, the present one *vs.* the one recently proposed by Abrahams [1].

Fourth, the current study embraced a retrospective, cross-sectional design, hence not allowing to draw inferences on the longitudinal course of FTSDs in non-demented ALS patients. However, as recently highlighted by one of the most comprehensive report to date [26], whether neuropsychological functions decline or not over time in this population is still a matter of debate—this prompting further investigations on the topic.

Fifth, this report did not employ psychodiagnostic instrument inquiring on depression and anxiety—both being moderately frequent in ALS patients and possibly exerting a moderating role on cognitive and/or behavioural manifestations [37, 38]. Most relevantly, the absence of such

measures did not allow disentangling the possible confounding effect of depressive symptoms from apathetic features—this being not a trivial matter given the partial overlap between depression and apathy [7]. It would be thus appropriate for future studies on the topic to also address psychopathological measures.

Sixth, no measures of functional independence—besides that specifically related to motor involvement (*i.e.*, the ALSFRS-R)—have been herewith taken into account. Hence, whilst a limited number of small-sized reports linked a greater degree of neuropsychological involvement to dependence in both basic and instrumental activities of daily living [39, 40], it is still advisable that future investigations explore this interplay on a large scale.

Seventh, whilst supporting the notion that the overall severity of motor-functional involvement might be linked to worse cognitive/behavioural outcomes in non-demented ALS patients, the current report did not focus on which specific motor features contribute the most to this association. Although previous investigations identified a number of motor characteristics being possibly associated with neuropsychological phenotypes in this population [28, 41–44], large-scaled studies that comprehensively explore this matter still needs to be performed.

Additionally, this study did not focus on the association between FTSDs and patients' genotypes. Besides the renowned role of the *C9orf72* hexanucleotide repeat expansion as a risk factor for frontotemporal involvement in this population [45], recent reports have delved into the neuropsychological phenotype of patients carrying other frequent pathogenic variants—such as *SOD1* and *TARDBP* [46–48]. Thereupon, further large-scaled investigations are needed that explore the prevalence and clinical presentation of FTSDs in ALS as a function of patients' genotype.

Finally, it should be acknowledged that the criteria here employed to a posteriori exclude patients being suspected of presenting with a previously undetected dementing syndrome exclusively relied on ECAS and ECAS-CI scores, whilst not on clinical history and information on functional independence. Whilst such an expedient has been embraced in the view of being as sure as possible that the present focussed solely on non-demented patients, this might as well have decreased the statistical power of the present findings—since a non-negligible number of cases were excluded accordingly (*i.e.*, 93 out of 901). At the same time, it would be reasonable to assume that the definite cohort having been addressed for the analyses is sufficiently large to grant a high degree of generalizability to the current findings.

## Conclusions

FTSDs affect ~50% of non-demented ALS patients, with cognitive deficits being as frequent as behavioural changes (~30%). The cognitive phenotype of these patients is mostly driven by dysexecutive features, followed by language and memory deficits. Apathy is the most frequently reported behavioural change. A higher degree of motor-functional involvement is associated with worse behavioural outcomes—with this link being weaker for cognitive deficits.

On a pragmatic level, this study highlights the importance of concurrently assessing both cognition and behaviour to properly capture the nature and extent of extra-motor, frontotemporal involvement in ALS, by also suggesting that patients with a more severe disease should be given particular attention as possibly being at a higher risk for behavioural changes.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00415-024-12658-w>.

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**Data availability** Datasets associated with the present study cannot be made publicly available as including sensitive information, but can be made available upon reasonable request of interested researchers to the Corresponding Author that will forward a data transfer agreement request to the relevant Ethical Committees. Raw data from the Corresponding Author’s primary Institution have been stored on an online repository with restricted access (<https://doi.org/10.5281/zenodo.13643093>).

## Declarations

**Conflict of interest** V. S. received compensation for consulting services and/or speaking activities from AveXis, Cytokinetics, Italfarmaco, Liquidweb S.r.l., and Novartis Pharma AG, receives or has received research supports from the Italian Ministry of Health, AriSLA, and E-Rare Joint Transnational Call. He is in the Editorial Board of *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, *European Neurology*, *American Journal of Neurodegenerative Diseases*, *Frontiers in Neurology*. B.P. received compensation for consulting services and/or speaking activities from Liquidweb S.r.l. B.P. is Associate Editor for *Frontier in Neuroscience*. N. T. received compensation for consulting services and/or speaking fees from Amylyx Pharmaceuticals, Biogen, Italfarmaco, and Zambon Biotech SA. He is Associate Editor for *Frontiers in Aging Neuroscience*. F.V. is Associated Editor for *Journal of Alzheimer’s Disease*. E.N.A. serves as an Editorial Board Member for *BMC Neurology*. A.Ch. is a member of the following Scientific Advisory Boards: Mitsubishi Tanabe, Roche, Biogen, Denali Pharma, Cytokinetics, Amylyx Pharmaceuticals, VectorY, and Ferrer and Zambon Biotech; he received a scientific grant from Biogen; he is a member of the following Drug Safety and Monitoring Boards: AB Science, Verge, Corcept and Eli Lilly; A. Ca. has received a research grant from Cytokinetics. The other authors have nothing to declare.

**Ethics approval** Participants provided informed consent and data were treated according to current regulations. This study was approved by the Ethics Committee of IRCCS Istituto Auxologico Italiano (ID: 2013\_06\_25), by the Ethics Committee of Fondazione IRCCS Istituto Neurologico Carlo Besta (ID: 71/2015; 2017/06/07, Excerpt 6/41; 2020/06/17, Excerpt 01/73; 2023/01/18, Excerpt 06/11), and by the Ethics Committee of the ALS Expert Center of Torino, Azienda Ospedaliero Universitaria Città della Salute e della Scienza (ID: #0038876).

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