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Cognitive-behavioral screening reveals prevalent impairment in a large multicenter ALS cohort

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Supplemental data at Neurology.org

ABSTRACT

Objectives: To characterize the prevalence of cognitive and behavioral symptoms using a cognitive/behavioral screening battery in a large prospective multicenter study of amyotrophic lateral sclerosis (ALS).

Methods: Two hundred seventy-four patients with ALS completed 2 validated cognitive screening tests and 2 validated behavioral interviews with accompanying caregivers. We examined the associations between cognitive and behavioral performance, demographic and clinical data, and *C9orf72* mutation data.

Results: Based on the ALS Cognitive Behavioral Screen cognitive score, 6.5% of the sample scored below the cutoff score for frontotemporal lobar dementia, 54.2% scored in a range consistent with ALS with mild cognitive impairment, and 39.2% scored in the normal range. The ALS Cognitive Behavioral Screen behavioral subscale identified 16.5% of the sample scoring below the dementia cutoff score, with an additional 14.1% scoring in the ALS behavioral impairment range, and 69.4% scoring in the normal range.

Conclusions: This investigation revealed high levels of cognitive and behavioral impairment in patients with ALS within 18 months of symptom onset, comparable to prior investigations. This investigation illustrates the successful use and scientific value of adding a cognitive-behavioral screening tool in studies of motor neuron diseases, to provide neurologists with an efficient method to measure these common deficits and to understand how they relate to key clinical variables, when extensive neuropsychological examinations are unavailable. These tools, developed specifically for patients with motor impairment, may be particularly useful in patient populations with multiple sclerosis and Parkinson disease, who are known to have comorbid cognitive decline. *Neurology*® 2016;86:813–820

GLOSSARY

ALS = amyotrophic lateral sclerosis; **ALSbi** = ALS with behavioral impairment; **ALSci** = ALS with cognitive impairment; **ALSFRS-R** = ALS Functional Rating Scale–Revised; **CBS** = Cognitive Behavioral Screen; **CNS-LS** = Center for Neurologic Study–Lability Scale; **COSMOS** = Multicenter Cohort Study of Oxidative Stress; **FBI** = Frontal Behavioral Inventory; **FTLD** = frontotemporal lobar dementia; **FVC** = forced vital capacity; **MMSE** = Mini-Mental State Examination; **MS** = multiple sclerosis; **NIEHS** = National Institute of Environmental Health Sciences; **PBA** = pseudobulbar affect; **PD** = Parkinson disease.

The past 2 decades are notable for heightened attention on cognitive and behavioral sequelae in neurologic diseases held to be previously exclusively motor in nature. Among patients with amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and Parkinson disease (PD) in particular, a continuum of neuropsychological changes has been identified. These previously undetected comorbid characteristics carry significant burden for patients, thus a consensus in the ALS field has emerged[1] to measure the broader spectrum of cognitive and behavioral changes as clinical trial outcomes.

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ALS COSMOS coinvestigators are listed on the *Neurology*® Web site at Neurology.org.

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Comprehensive neuropsychological evaluations identify frank ALS dementia at rates of 8% to 15%.[2–4] Larger fractions exhibit mild to moderate deficits, with ALS with cognitive impairment (ALSci) occurring in 34% to 51%[3–8] and ALS with behavioral impairment (ALSbi) occurring in 13.9% to 40%[4,9,10] of patients.

Recently validated screening tools mirror impairment rates seen with gold standard neuropsychological batteries. These include the ALS Cognitive Behavioral Screen (CBS) (57%),[11] the Edinburgh Cognitive and Behavioural ALS Screen (23%–35%),[9] and the Penn State cognitive screen (22%–36%).[12] Among behavioral screens, the Cambridge Behavioural Inventory,[13] ALS Frontotemporal Dementia Questionnaire,[2] and the Motor Neuron Disease Behavioural Instrument[14] find behavioral changes in 80%, 17%, and 58%–75% of samples, respectively.

Herein, we report baseline assessment of patients in the ALS Multicenter Cohort Study of Oxidative Stress (COSMOS): the first prospective, multicenter investigation of the role of oxidative stress in disease progression.[15]

METHODS

The patient population, methodology, and early findings of the COSMOS study are reported elsewhere.[15] Among 355 patients enrolled in the ALS COSMOS study, 26 diagnosed with PMA or presumed PLS (pure lower or upper motor neuron disease) were excluded from the analyses. Fifty-five patients enrolled before the inclusion of the cognitive assessment were also excluded. Two hundred seventy-four patients were diagnosed as "definite," "probable," or "possible" by the El Escorial/Airlie House revision,[16] with the addition of the Awaji Criteria, to increase the chance of early diagnosis.[17] Participants had no history of ALS in immediate family members and were enrolled within 18 months after symptom onset.

Two cognitive screening measures were administered to patients and 2 behavioral questionnaires were administered to caregivers, each having been previously validated in ALS[11,18,19] or frontotemporal lobar dementia (FTLD) populations.[20] Standardized test administration training was performed at investigator's meetings or by phone. Printed and video training materials created by J.M. were distributed to all centers.

Screening measures for cognitive functioning. ***ALS CBS cognitive subscale.*** This test, yielding a total cognitive score ranging from 0 to 20 (ALS CBS-Cog), is generated from 4 subtests: initiation and retrieval, concentration, attention, and tracking-monitoring. Participants with ALS CBS total cognitive scores below the cutoff for dementia (≤10) were classified as possible FTLD, cognitive type, and those scoring within the cutoff range for cognitive impairment (11–16) were classified as ALSci. Those scoring 17 and above were classified as cognitively normal.

Written verbal fluency test (C-Words). This measure requires patients to generate written words beginning with the letter C, with time constraints and limitations on the number of letters permitted. "Thinking time" is calculated by adjusting the score of the patient's writing speed, controlling for both dysarthria and hand weakness.[18]

Behavioral functioning. ***ALS CBS behavior subscale.*** This questionnaire rates changes perceived in the patient by the caregiver, categorizing level of behavioral change based on established norms. Scores below the cutoff (≤32) were classified as possible FTLD, behavioral type. Those scoring in the impaired range (33–36) were classified as ALSbi, and those scoring 37 and above as behaviorally normal. We used a reversed-scoring form of the subscale, with abnormal behavior scores earning more points. The equivalent standard published cutoffs are provided here for ease of comparison.

Frontal Behavioral Inventory—ALS version. Trained raters interviewed caregivers to distinguish between frontal lobe–based behavior change and changes secondary to motor neuron disease, using this revised version of the original Frontal Behavioral Inventory (FBI).[19,20] Behavior change was rated from 0 to 3 on 24 items, grouped into negative behavior and disinhibition subscales.

Table 1 Outcome measures' associations with demographic variables using multiple regression procedures

Outcome measures	Age	Sex	Education	Race	Duration of symptoms	Diagnostic certainty
ALS CBS-cognitive	−0.053, 0.020, 0.008[a]	−0.170, 0.394, 0.651	0.995, 239, <0.001[a]	0.277, 0.696, 0.691	−0.712, 0.502, 0.157	−0.288, 0.250, 0.250
Verbal Fluency Index	0.406, 0.268, 0.133	−10.65, 5.22, 0.043[a]	−4.54, 3.07, 0.142	9.22, 9.55, 0.336	3.80, 6.75, 0.574	0.098, 3.26, 0.976
ALS CBS-behavioral	0.033, 0.041, 0.424	0.340, 0.846, 0.689	−0.949, 0.512, 0.065	0.742, 1.49, 0.619	−0.335, 1.09, 0.758	0.636, 0.538, 0.238
FBI-ALS	0.001, 0.045, 0.976	0.204, 0.915, 0.824	−0.862, 0.550, 0.118	−1.65, 1.65, 0.320	1.35, 1.18, 0.253	1.16, 0.582, 0.047[a]
MMSE	−0.027, 0.011, 0.020[a]	0.469, 0.233, 0.046[a]	0.495, 0.142, 0.001[a]	−0.136, 0.403, 0.736	−0.489, 0.298, 0.102	−0.018, 0.149, 0.902
CNS-LS	−0.066, 0.031, 0.036[a]	0.960, 0.625, 0.126	−1.33, 0.381, 0.001[a]	−0.607, 1.09, 0.580	1.17, 0.802, 0.148	1.03, 0.399, 0.010[a]

Abbreviations: ALS = amyotrophic lateral sclerosis; CBS = Cognitive Behavioral Screen; CNS-LS = Center for Neurologic Study–Lability Scale; FBI = Frontal Behavioral Inventory; MMSE = Mini-Mental State Examination.
Data represent B (coefficient), SE, and *p* value.
[a] Indicates significance.

Supplemental measures. ***The Center for Neurologic Study–Lability Scale.*** This patient self-report measure characterizes pseudobulbar affect (PBA) symptoms using a simple rating scale.[21] The pathologic cutoff score of 13 and above diagnosed the presence of clinically significant PBA.

Folstein Mini-Mental State Examination. The most widely used routine brief screen provides a global cognitive score.[22]

Clinical assessments included respiratory capacity (forced vital capacity [FVC]) and a measure of functional status (ALS Functional Rating Scale–Revised [ALSFRS-R]). Blood samples for DNA and other biomarkers were collected and stored in the National Institute of Environmental Health Sciences (NIEHS) Center for Environmental Health in Northern Manhattan Biorepository. DNA was analyzed for *C9orf72* mutations in the 251 patients for whom we had both cognitive and DNA data. All data were stored in the Data Management Center at the Columbia University Medical Center.

Statistical analyses. Associations between demographic variables, cognitive and behavioral variables, and *C9orf72* status were assessed using Spearman correlation, multiple regression, and analysis of covariance, as appropriate. Multivariate procedures always included the covariates of age, sex, duration of symptoms, education, race, ethnicity (Hispanic, not Hispanic), and diagnostic certainty. The association between bulbar functioning and cognitive-behavioral decline was tested using regression procedures controlling for age, sex, duration of disease, education, race, and ethnicity. Total FBI-ALS score was correlated continuously with cognitive and clinical variables. When examining the individual items of the FBI-ALS and ALS CBS behavior subscale for specific associations with cognition, we used a multiple regression with forward and backward selection. For these, the a priori covariates were entered at the first step, followed by the items at subsequent steps. All significance levels were set at $p \leq 0.05$.

Standard protocol approvals, registrations, and patient consents. Institutional review board approval was obtained from the Columbia University Medical Center and from each clinical site. All patients determined by screen to have the cognitive capacity gave written informed consent. Each of the screening tests was obtained with permission of the authors, is noncopyrighted, and is freely available for noncommercial use.

RESULTS

Cognitive and behavioral impairment rates. Cognitive impairment consistent with possible FTLD occurred in 6.5% of the patients. Scores consistent with ALSci were found in 54.2% of patients, and 39.2% of patients were in the normal range. Behavioral impairment consistent with possible FTLD occurred in 16.5% of the patients. Scores consistent with ALSbi range were found in 14.1% of patients, and 69.4% of patients were in the normal range.

Key demographic and clinical correlates of cognitive and behavioral measures. Each cognitive and behavioral outcome measure was regressed on the following possible predictors: age, sex, race/ethnicity, education, duration of symptoms, and diagnostic certainty (possible, probable, definite; table 1).

Behavioral impairment but not cognitive impairment was associated with functional status, respiratory function, region of onset, and PBA (table 2). A closer examination of the ALS CBS cognitive subscales found that none of the individual scales were associated with breathing status, after being controlled for the covariates. Clinically significant PBA was identified in 50.8% of the patients using a cutpoint of 13 and greater for the Center for Neurologic Study–Lability Scale (CNS-LS) score. The continuous CNS-LS score was significantly associated with the ALS CBS behavioral scores ($p < 0.001$, more lability with more behavioral problems) and the FBI-ALS ($p = 0.018$).

Relationship between cognitive and behavioral functioning. A more impaired FBI total was significantly associated with a more impaired ALS CBS cognitive total when controlling for age, sex, duration of symptoms, education, race/ethnicity, and diagnostic certainty (B = −0.066, SE = 0.028, $p = 0.018$). When ALSFRS-R and FVC% were added to this model, this association was attenuated (B = −0.050, SE = 0.030, $p = 0.092$). Similarly, a better ALS CBS behavioral total was negatively associated with a worse ALS CBS cognitive total (B = −0.120, SE = 0.031, $p < 0.001$), controlling for the same variables, suggesting that better behavioral scores were associated with better cognitive scores.

Table 2 Relationship between cognition/behavior and clinical variables

Outcome measures	Respiratory function (FVC), B, SE, *p*	Functional status (ALSFRS-R), B, SE, *p*	Pseudobulbar affect (CNS-LS), B, SE, *p*	Region of onset, *F*, *p*
ALS CBS-cognitive	0.014, 0.009, 0.130	0.003, 0.034, 0.920	−0.076, 0.041, 0.067	1.03, 0.358
Verbal Fluency Index	−0.004, 0.005, 0.381	0.011, 0.019, 0.573	0.004, 0.020, 0.849	0.46, 0.634
ALS CBS-behavioral	−0.053, 0.020, 0.008[a]	−0.221, 0.071, 0.002[a]	0.351, 0.085, <0.001[a]	6.60, 0.002[a]; adjusted means (SE): Bulbar = 7.6 (0.71), spinal = 4.9 (0.49), other = 11.3 (2.80)
FBI-ALS	−0.056, 0.021, 0.008[a]	−0.127, 0.077, 0.098	0.222, 0.094, 0.018[a]	1.68, 0.190

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale–Revised; CBS = Cognitive Behavioral Screen; CNS-LS = Center for Neurologic Study–Lability Scale; FBI = Frontal Behavioral Inventory; FVC = forced vital capacity.
Multiple regression procedures were applied, controlling for age, sex, duration of symptoms, education, race/ethnicity, and diagnostic certainty. For region of onset, analysis of covariance was applied.
[a] Indicates significance.

Table 3 Examination of ALS behavioral impairment criteria by ALS cognitive impairment criteria, shown as number of cases (%) (within cognitive impairment group)

ALS behavioral impairment	ALS cognitive impairment			
	None	ALSci	FTLD	Totals
None	71 (75.5)	95 (69.9)	8 (47.1)	174 (70.4)
ALSbi	10 (10.6)	22 (16.2)	2 (11.8)	34 (13.8)
FTLD	13 (13.8)	19 (14.0)	7 (41.2)	39 (15.8)
Totals	94 (100.0)	136 (100.0)	17 (100.0)	247 (100.0)

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSbi = ALS with behavioral impairment; ALSci = ALS with cognitive impairment; FTLD = frontotemporal lobar dementia.
$\chi^2 = 10.42$, $df = 4$, $p = 0.034$.

We also examined the combined ALS-Cog and the ALS-Beh impairment criteria in a 3 × 3 cross-tabulation (n = 247; table 3) and found that 28.7% of the cases were normal for both, 8.9% met the multidomain ALSci/ALSbi criteria, and 2.8% met the FTLD criteria for both. While 70.4% of the cases (174/247) were normal for ALS-Beh, only 38% of the cases were cognitively normal. Among those with no cognitive impairment, 75.5% also had no behavioral impairment; however, 10.6% had ALSbi and 13.8% FTLD. However, among those with cognitive FTLD, only 47.1% had no behavioral impairment with 11.8% and 41.2% having ALSbi and FTLD, respectively. This demonstrates substantial comorbidity ($\chi^2 = 10.42$, $df = 4$, $p = 0.034$).

To identify specific symptoms driving the associations between the behavioral and cognitive scores, we found 8 unique behaviors endorsed by caregivers as occurring in more than 25% of the sample (table 4).

Table 4 Common behavioral problems (reported as ≥25%) and relationship with poorer cognition

	High rates of prevalence, %
FBI-ALS items	
Irritability	38.0
Inflexibility	27.1
Apathy	26.7
ALS CBS-behavior subscale	
Irritability	65.6
Poor frustration tolerance	48.4
More withdrawn	38.8
Less agreeable	36.1
More confused	34.9
	Items' association with lower cognition association: B, SE, *p*
FBI-ALS items	
Aphasia/apraxia	Higher: −0.837, 0.298, 0.005
Disorganization	Higher: −0.743, 0.317, 0.020
Logopenia	Higher: −0.658, 0.326, 0.045
Indifference/emotional flatness	Higher: −0.770, 0.282, 0.007
Inattention	Lower: 1.301, 0.319, <0.001
Inappropriateness	Lower: 1.465, 0.640, 0.023
Aggression	Higher: −1.109, 0.499, 0.027
Hypersexuality	Higher: −2.186, 0.779, 0.005
ALS CBS-behavior subscale	
Less interest in topics/events	Higher: −0.558, 0.262, 0.034
Less concerned about feelings of others	Higher: −1.108, 0.319, 0.001

Abbreviations: ALS = amyotrophic lateral sclerosis; CBS = Cognitive Behavioral Screen; FBI = Frontal Behavioral Inventory.
A multiple regression-backward selection procedure was used, controlling for age, sex, duration of symptoms, education, race/ethnicity, and diagnostic certainty.

***C9orf72* hexanucleotide repeats.** *C9orf72* repeat expansions were found in 5.6% of the participants with cognitive and genetic data. Slightly higher rates of positive C-9 status were found in females compared to males (9.0% vs 3.3%; $p = 0.055$). After controlling for the covariates, the association became stronger ($p = 0.014$). *C9orf72* status was not associated with levels of cognitive impairment or behavioral impairment on the ALS CBS (ALS CBS-Cog Fisher exact test = 0.808, ALS CBS-Beh Fisher exact test = 0.068), the FBI-ALS total (Fisher exact test = 1.00), or the Verbal Fluency Index (Fisher exact test = 0.668).

Sampling and concurrent validity. Comparisons of the 274 patients tested cognitively with 55 not tested revealed no differences in age, duration of illness, ALSFRS-R, FVC, sex, or education (table 5). The group given all cognitive screening tests scored 0.7 point lower on the Mini-Mental State Examination (MMSE), which is not clinically meaningful although statistically significant ($p < 0.001$).

To assess the possible role of variable recruitment numbers on scores, we grouped enrollment sites by recruitment rate: 2 patients/month ("highest"), between 0.5 and 2 per month ("high"), and below 0.5 per month ("low"). Total cases enrolled at each site served as a covariate. No differences in the 4 outcome measures were found between site groups, even after controlling for demographic covariates and total number of cases enrolled. The MMSE significantly differed between site groups (adjusted means [SE]: highest enroller = 27.73 [0.564], high enroller = 29.35 [0.174], and low enroller = 29.32 [0.462]; $p = 0.010$) although post hoc tests revealed a significant difference only between the highest and the high enroller sites.

Concurrent validity was assessed as the within cognitive or within behavioral correlations between the 2 measures of each construct. The 2 behavioral measures were highly correlated (FBI-ALS behavior scores and ALS CBS behavior scores, $r = 0.721$, $p < 0.001$), and the 2 cognitive measures moderately so

Table 5 Summary of demographic, clinical, cognitive, and behavioral screening tests among ALS cases with cognitive data and ALS cases without cognitive data

	ALS cases with screening (n = 274)[a]	ALS cases without screening (n = 55)	*p* Values
Demographic variables			
Age, y, mean (SD)	60.5 (10.1)	62.1 (11.3)	0.293
Sex, % female	41.6	36.4	0.470
Education, %	n = 273	n = 50	
High school or less	24.2	30	
Trade/associates degree/some college	31.9	18	
BA/BS and higher	44.0	52	0.141
Race, %	n = 261	n = 52	
White	91.6	82.7	
Nonwhite	8.4	17.3	0.050
Clinical evaluation, mean (SD)	n = 274	n = 55	
Duration of symptoms, mo	11.8 (4.5); n = 252	11.3 (4.3); n = 54	0.445
FVC%	79.4 (22.8); n = 266	77.5 (23.8); n = 39	0.596
ALSFRS-R	36.1 (6.6)	34.6 (8.0)	0.279
Region of onset, %	n = 274	n = 55	
Bulbar	32.1	34.5	
Cervical	32.5	38.2	
Thoracic	1.1	0.0	
Lumbosacral	32.1	27.3	
Respiratory	1.8	0.0	
Other	0.4	0.0	0.749
MMSE score	28.9 (1.8)	29.6 (0.66)	0.001

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale–Revised; FVC = forced vital capacity; MMSE = Mini-Mental State Examination.
[a] Numbers vary due to attainment.

(written verbal fluency and the ALS CBS cognitive score, $r = 0.494$, $p < 0.001$).

DISCUSSION We used a brief cognitive and behavioral screening battery with 274 patients with ALS. FTLD-level dementia and mild to moderate impairment were prevalent, with more than a third of patients having cognitive or behavioral decline. The rate of possible FTLD-level dementia was higher when behavioral symptoms were measured (16.5%) as compared to cognitive symptoms (6.5%) alone. These rates are consistent with other investigations[9,12,13,23] but our large sample size and clear differentiation between cognitive and behavioral impairment make this a novel contribution. The rate of symptoms consistent with ALSci level of impairment were commensurate with the literature (ALSci: 54.2%) and higher than caregiver reports of ALSbi-level rates of behavior change (ALSbi: 14.1%). Few studies have clear differentiated cutoffs for ALSbi vs ALS-FTLD, and these data suggest that when patients have behavioral changes, caregivers describe it as being more severe than mild in nature.

Concurrent validity was moderate to strong, supporting the strategy of using 2 screening tools for each domain: one narrow, specific measurement tool together with a broader, more inclusive tool, to capture a full range of data for cognition and behavior. The data indicate that this short screening battery is acceptable and highly useful in a large multicenter study. Our results were consistent across a variety of large and modest sites across the country, indicating that if evaluators are well trained, the screening battery is practicable for use in neurologic trials.

Understanding how the ALS process affects cognition and behavior will lead to understanding of its etiology. The literature has been unclear about whether cognitive-behavioral impairment is caused by decreased respiratory capacity, for example,[24] but our findings demonstrate no relationship between respiratory function and cognitive behavioral decline. This supports the theory that these deficits are neurologic in nature and not merely the secondary effects of hypoxia. The hypoxia connection[25] was further invalidated by analyses that showed no association between FVC and the 4 cognitive subtests. This lack of correlation was obtained after carefully controlling for clinical and demographic covariates.

Behavioral but not cognitive impairment was associated with ALS functional decline. Apathy and logopenia were the only behavioral symptoms statistically associated with ALSFRS-R. This association was strongest for the bulbar subscale, with greater levels of apathy and logopenia being reported in participants with more bulbar pathology. The literature is conflicted[26] regarding whether bulbar-onset patients have greater levels of frontotemporal symptoms, with few studies having the statistical power to separate cognitive from behavioral functioning. In this investigation, behavioral and not cognitive deficits are associated with bulbar deficits. Apathy has been singled out as a uniquely important behavioral variable, being the most common behavior change in patients with ALS.[10,12,27] In this study, caregivers reported that 27% to 66% of participants showed increased levels of irritability, inflexibility, poor frustration tolerance, emotional indifference, and apathy severe enough to impose increased burden on caregivers' ability to assist patients. Patients' reduced initiation and decreased motivation to comply pose considerable caregiving challenges in this rapidly progressing disease.

Patients presenting with emotional indifference, aphasia/apraxia, and logopenia were likely to possess comorbid cognitive problems. This particular constellation of behavioral changes is reminiscent of "negative symptoms" seen in schizophrenia, in that they represent the absence of expected behavior, or an "apathetic"

subtype. Of note, behavioral traits of inappropriateness and inattention were associated with higher cognitive functioning, suggesting a unique cluster of behaviors unrelated to cognitive decline. Inappropriateness in particular is suggestive of a "disinhibited subtype" of patient with less cognitive impairment, in contrast to an "apathetic" counterpart with cognitive decline. This interpretation would be consistent with the FTLD literature's separation of these subtypes and is worthy of future study. If future research supports these subtypes, apathetic patients may signal to clinicians a need for cognitive evaluation and treatment accommodations, while disinhibited patients may have fewer cognitive deficits.

PBA is an important clinical variable to measure in neurologic disease populations, particularly in ALS, MS, and cerebrovascular accident. We identified a high prevalence of PBA in this sample (50.8%), and 3 of the 4 outcome measures were associated with PBA, with worse cognition (ALS CBS-Cog) and more behavior problems (ALS CBS-Beh and FBI-ALS) being significantly correlated with higher levels of PBA. Patient ratings of PBA were associated with caregiver ratings of problems with apathy, excessive jocularity, and hypersexuality. While excessive jocularity is consistent with laughing spells, the relationship between PBA, apathy, and hypersexuality is less clear. The link between PBA and apathy may be more complex, as we found an association between apathy and bulbar functioning on the ALSFRS bulbar subscale.

C9orf72-positive status is of interest in cognitive and behavioral ALS studies because of its association with FTLD.[28] In this investigation of patients with sporadic ALS, 5.6% had positive *C9orf72* status, yet we did not detect an association with increased levels of cognitive impairment or behavioral impairment, possibly because of the small number of *C9orf72* cases.

While the large majority of at-diagnosis cognitively normal patients with ALS have a low risk of a frank dementia syndrome, a majority of patients may possess mild to moderate cognitive and behavioral changes. This investigation is consistent with other reports of overlapping symptoms of cognitive and behavioral change.[10] These data provide clinically relevant evidence that patients with bulbar-onset ALS, comorbid PBA, reduced breathing function, and reduced functional status are all more likely to have comorbid behavioral problems.

Cognitive screening tests cannot replace a definitive diagnostic neuropsychological examination, which requires a multihour neuropsychological battery and clinical interview with clinicians trained in diagnosing FTLD (table e-1 on the *Neurology*® Web site at Neurology.org). Nevertheless, our study using a well-validated cognitive screening test demonstrates overall rates of cognitive and behavioral impairments comparable to those found in full neuropsychological testing. Application of this type of screening battery could extend beyond ALS to other diseases with executive functioning syndromes (e.g., MS, PD), including those in which extramotor involvement is commonly known but standardized screens are lacking (e.g., Huntington disease, multiple systems atrophy, Lewy body dementia, progressive supranuclear palsy, and corticobasal degeneration). Rapid and accurate detection in these and other conditions would allow triage services early in the disease course, which could influence patient/family education and prognostication. The ALS CBS is likely the best of these screening tests for routine clinical application because it provides examination of multiple domains without requiring extensive staffing resources.

Identifying cognitive function in motor neuron diseases has become more important as patients with cognitive impairment have shorter survival.[29,30] Furthermore, stratifying patients by cognitive status can lead to significant improvements in clinical trials.[31] However, the standard methods of multihour neuropsychological examinations are frequently unavailable in busy clinics and impractical in clinical research. Our testing battery provides neurologists with a simplified approach that (1) adjusts cognitive tests to remove the effects of dysarthria and hand weakness, (2) adjusts behavioral interviews to account for physiologic changes associated with diseases affecting motor function, and (3) provides a sensitive and valid measure of the cognitive and behavioral deficits in a nondemented neurologic sample. A telephone-based cognitive screening battery is being developed to further increase the accessibility of the testing (Christodoulou, abstract).

AUTHOR CONTRIBUTIONS

Dr. Jennifer Murphy is the primary and corresponding author. Dr. Pam Factor-Litvak assisted as the co-PI and was involved with the planning, statistical analyses, as well as analyses of biomarkers, exposures, and cognition. She also prepared drafts of the manuscript. Dr. Raymond R. Goetz played a major role in the general statistical analyses in addition to preparing drafts of the manuscript. Dr. Cathy Lomen-Hoerth served as site investigator for the University of California San Francisco and was involved in planning the study, data collection, and reviewing the manuscript. Dr. Peter L. Nagy assisted in analyses of biomarkers in addition to reviewing the manuscript. Jon Hupf, MA, assisted in the planning and coordination of the study, data collection, and reviewing the manuscript. Jess Singleton, MA, assisted in coordination of the study, data collection, and reviewing the manuscript. Dr. Susan Woolley was involved in the planning of the cognitive analyses and in reviewing the manuscript. Dr. Howard Andrews assisted in data management for the entire study in addition to reviewing the manuscript. Dr. Daragh Heitzman served as the site investigator at Texas Neurology in Dallas. He has been involved in planning the study, patient evaluations, data collection, and data analysis. He is serving as the Databank and Biobank Committee Chairperson for the ALS COSMOS Study. Dr. Richard S. Bedlack served as site investigator for Duke University, and was involved with planning of the study, data collection, and reviewing the manuscript. Dr. Jonathan S. Katz served as the site investigator at California Pacific Medical Center.

Dr. Richard J. Barohn served as site investigator for the University of Kansas and was involved with planning of the study, data collection, and reviewing the manuscript. Dr. Eric J. Sorenson served as site investigator for Mayo Clinic, Rochester, and was involved with planning of the study, data collection, statistical analysis, and reviewing the manuscript. Dr. Björn Oskarsson served as site investigator for University of California, Davis, and was involved with planning of the study, data collection, statistical analysis, and reviewing the manuscript. Dr. J. Americo M. Fernandes Filho served on the publication committee of the project and reviewed the manuscript. Dr. Edward J. Kasarskis served as site investigator for University of Kentucky and was involved with planning the study, data collection, and reviewing the manuscript. Dr. Tahseen Mozaffar served as site investigator for University of California, Irvine, and was involved with data collection and reviewing the manuscript. Dr. Yvonne Rollins served as a site investigator for the University of Colorado. Dr. Sharon P. Nations served as site investigator for University of Texas, Southwestern, was involved with planning of the study, data collection, and reviewing the manuscript. Dr. Andrea J. Swenson served as site investigator for University of Iowa Hospitals and Clinics and was involved in subject recruitment. Dr. Boguslawa A. Koczon-Jaremko served as site investigator for Hospital for Special Care, New Britain, CT, and was involved with data collection and reviewing the manuscript. Dr. Hiroshi Mitsumoto served as the primary investigator for this study. He was involved in all stages of this project, data collection, analyses, and preparing the draft of the manuscript.

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DISCLOSURE

J. Murphy is employed by the CRO INC research. P. Factor-Litvak, R. Goetz, C. Lomen-Hoerth, P. Nagy, J. Hupf, J. Singleton, S. Woolley, and H. Andrews report no disclosures relevant to the manuscript. D. Heitzman has received financial support from the Muscular Dystrophy Association for the ALS MDA Center at Texas Neurology. He has received research support from National Institutes of Health (via Columbia University Subcontract), Biogen Idec, Questcor Pharmaceuticals, Merz Pharmaceuticals, and Cytokinetics for research trials in which he was the site investigator. R. Bedlack has research grants from the ALS Association, Motor Neurone Disease Association, and Cytokinetics, and is a paid consultant for the ALS Association and Neuraltus Pharmaceuticals. J. Katz, R. Barohn, and E. Sorenson report no disclosures relevant to the manuscript. B. Oskarsson is a speaker for Grifols, his research is supported by Novartis, Cytokinetics, the ALS Association, NIH UL1 TR 000002, and linked award KL2 TR 000134, NINDS U10 NS077422-01, and NINDS 1 U01 NS049640-02, serves on the Board of the Greater Sacramento ALS Association, and he practices clinical neuromuscular medicine and bills for this. J. Fernandes Filho and E. Kasarskis report no disclosures relevant to the manuscript. T. Mozaffar has received personal compensation from consulting activities to Baxter, Biogen Idec, BioMarin, California Stem Cell Inc., Crescent (a Walgreens company), CSL Behring, Genzyme, Grifols, Idera, NuFactor, and Ultragenyx. Dr. Mozaffar received funding from NIH (NS049203) and received clinical research support from ALSTDI, Alexion, Alnylam, Amicus, Biogen Idec, BioMarin, CSL, Cytokinetics, FDA, Grifols, Genzyme, GSK, ISIS, Neuraltus, Novartis, and Ultragenyx. Dr. Mozaffar is currently serving as the chair of the medical advisory board for the Myositis Association. Y. Rollins, S. Nations, A. Swenson, and B. Koczon-Jaremko report no disclosures relevant to the manuscript. H. Mitsumoto received research support from SPF, MDA Wings Over Wall Street, NIEHS (R01ES016348), and private donations from Mr. and Mrs. David Marren. Go to Neurology.org for full disclosures.

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