APATHY, DEPRESSION, AND EMOTIONAL LABILITY IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

A Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Whitney Havins

August, 2014

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ABSTRACT

The presence of cognitive and behavioral impairment in some patients with amyotrophic lateral sclerosis (ALS) is now well-known. However, the prevalence of behavioral impairment and the relationship between behavioral and cognitive impairment in ALS is not fully understood. This study is the first to examine systematically cognitive profiles associated with apathy, depression, and emotional lability (EL) in patients with ALS. Participants were 161 consecutive referrals to the Neurology service of the Houston Methodist Hospital MDA-ALS clinic. All patients met El Escorial World Federation of Neurology diagnostic criteria for probable or definite ALS. All participants underwent comprehensive neuropsychological evaluation, including measures of cognition, mood, and behavior. Multiple hierarchical regression analyses were used to predict performance on neuropsychological measures from apathy, depression, and emotional lability. Of the 161 patients, 24.8% were diagnosed with EL and 18.6% met criteria for DSM-IV-*TR* diagnosis of a mood disorder (including 9.9% with a Major Depressive Disorder (MDD) or Dysthymia and 8.7% with an adjustment disorder). Of the 117 with complete apathy data, 32.5% met criteria for clinically significant apathy. Approximately 22% of patients were experiencing two or more of these neuropsychiatric disorders. After controlling for disease severity, apathy accounted for significant variance in predicting performance on a measure of mental flexibility, over and above depression and emotional lability. Neither MDD nor EL significantly predicted performance on any neuropsychological measure. Results suggested that apathy, depression, and emotional lability co-occur, but are dissociable in ALS. After controlling for disease severity, only apathy was associated with executive functioning.

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Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal, neurodegenerative disease involving both upper and lower motor neurons. The diagnosis is one of exclusion and typically includes electrophysiological, clinical laboratory, neuropathological, and neuroimaging evidence to rule out other causes of motor neuron dysfunction. It has a prevalence rate of approximately 4 per 100,000 and an annual incidence rate of about 1 per 100,000 (Tsermentseli, Leigh, & Goldstein, 2012). ALS is most commonly sporadic, with familial ALS representing only 10% of all patients (Norris, Que, & Bayat, 2010). The incidence of the disease increases with age, with a peak occurrence between 55 and 75 years of age. There is evidence that sporadic ALS is more common in men than in women, particularly for those patients with earlier age at disease onset (McCombe & Henderson, 2010). The mean duration of disease is approximately 3–4 years. Although primarily a motor system disorder, it is now well known that ALS is a multisystem disorder associated with cognitive impairment and behavioral and emotional changes.

Table 1. El Escorial World Federation of Neurology Criteria for the Diagnosis of ALS

The diagnosis of ALS requires:

(A) the **presence** of:

(1) evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathological examination,
(2) evidence of upper motor neuron (UMN) degeneration by clinical examination, and
(3) progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination, together with:

(B) the **absence** of:

(1) electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration, and
(2) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

Reproduced from Brooks, R.B., Miller, R.G., Swash, M., & Munsat, T.L. (2000). El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. *ALS and other motor neuron disorders, 1*, 293-299.

Cognitive Impairment in ALS

Cognitive impairment in ALS has been described as ranging from subtle cognitive deficits to severe impairment consistent with dementia. Up to 50% of patients with ALS experience some degree of cognitive impairment, most often in executive functioning, and in particular, phonemic fluency (Grossman, Woolley-Levine, Bradley, & Miller, 2007; Massman et al., 1996; Palmieri et al., 2009; Ringholz et al., 2005; Schreiber et al., 2005; Strong et al., 2009). In addition, many authors have reported ALS patients to have deficits in other cognitive domains, including language, attention, and memory. ALS with cognitive impairment is now recognized as a subtype of ALS (abbreviated ALS*ci*; Strong et al., 2009). Raaphorst, de Visser, Linssen, de Han, and Schmand (2010) conducted a meta-analysis to clarify the cognitive profile of non-demented patients with ALS. Based on 16 studies containing 554 participants with possible, probable, or definite ALS, the authors found the following impairments in decreasing order of effect sizes: Mini Mental State Examination (MMSE), psychomotor speed, fluency, language, visual memory, immediate verbal memory, and executive functioning. No significant impairments were found for verbal IQ, delayed verbal memory, attention, visuoperception, or visuoconstruction. This pattern of deficits may progress to more prominent language and executive dysfunction characteristic of frontotemporal lobe dementia (FTD). In fact, approximately 22% of ALS patients develop FTD (Lomen-Hoerth et al., 2003; Murphy et al., 2007), and the substantial co-occurrence of ALS and FTD, the overlap in cognitive profiles, and their shared neuropathology suggests that these diseases exist on a continuum (Lomen-Hoerth, 2011). Appendix 1 provides a more detailed summary of previous cognitive findings in ALS. Studies included in the table met the following criteria: 1) inclusion of participants with a diagnosis of ALS made according to

validated clinical criteria (e.g., El Escorial criteria), 2) exclusion of patients with multiple etiologies (or data from patient with ALS were analyzed separately), 3) control group or clearly stated normative standards, 4) at least one neuropsychological test, and 5) at least 10 participants with ALS. If the study was longitudinal, data from the first time point were included in the table.

Clinical evidence of cognitive impairment in ALS is supported by neuroimaging and neuropathological findings of extramotor involvement in ALS patients with and without cognitive deficits (Chang et al., 2005). Studies investigating the cerebral basis for cognitive dysfunction in non-demented patients with ALS have consistently demonstrated structural and functional abnormalities in the prefrontal, frontal, and temporal cortices (Abe et al., 1997; Abrahams et al., 2004; Evdokimidis et al., 2002; Hanagasi et al., 2002; Ludolph et al., 1991; Mezzapesa et al., 2007; Pinkhardt et al., 2008), as well as diminished activation along a limbo-thalamo-cortical pathway (Kew et al., 1993) and other subcortical structures (Ludolph et al., 1991). Mezzapesa and colleagues (2007) found that brain parenchymal fraction (BPF; ratio of brain parenchymal volume to intracranial volume) was significantly lower in ALS patients than in controls, even after controlling for age and sex. Moreover, cognitive impairment was significantly associated with lower BPF in patients with ALS. Abrahams et al. (2004) used functional magnetic resonance imaging (fMRI) to compare activation of ALS patients and healthy controls while patients performed classic neuropsychological tasks. During a letter fluency task, ALS patients showed impaired activation in the dorsolateral regions of the prefrontal cortex and anterior cingulate gyrus, as well as abnormalities in the middle temporal gyrus, precuneus, and inferior parietal lobes. In addition, performance on a confrontation naming task was associated with reduced activation

in the inferior frontal gyrus, middle and superior temporal gyri, middle occipital lobes, and cuneus of ALS patients. Of note, ALS and control patients were not significantly different on these tasks, meaning that performance variables (e.g., underlying cognitive ability, number of images correctly named, number of words produced) could not account for these findings. Lastly, a few small regions of increased activation were observed in ALS participants, suggesting selective reduction in specific brain regions, rather than an overall reduction in activity. Evidence from years of neuropathological studies is consistent with these imaging studies, detailing pathology (e.g., atrophy, ubiquitinated inclusions, and rarefaction) in frontotemporal areas with major connections to posterior, subcortical and limbic structures (Tsermentseli et al., 2012). Ultimately then, the evidence supports a frontotemporal pattern of extramotor involvement in ALS that may explain the cognitive impairments reported in the literature and observed clinically.

It has been suggested that cognitive impairment adversely affects ALS patients' quality of life. Goldstein, Atkins, and Leigh (2002) argue that cognitive difficulties may be even more detrimental to quality of life than physical impairment. Cognitive impairment can negatively impact decision-making abilities, treatment compliance, survival, and caregiver well-being (Jelsone-Swain et al., 2012). Cognitive impairment has been associated with male gender (Irwin, Lippa, & Swearer, 2007; Portet, Cadilhac, Touchon, & Camu, 2001), lower levels of education (Irwin et al., 2007, Massman et al., 1996), disease severity (Massman et al., 1996), disease duration (Frank, Haas, Heinze, Stark, & Münte, 1997), dysarthria (Massman et al., 1996), respiratory dysfunction (Strutt et al., 2012), bulbar onset (Gordon et al., 2011; Irwin et al., 2007; Schreiber et al., 2005; Strong et al., 1999), and pseudobulbar palsy (Abrahams et al., 1997). Given the paucity of longitudinal data, it is unclear whether

these cognitive impairments worsen with the disease (Phukan, Pender, & Hardiman, 2007). Most studies to date have reported that cognitive deficits appear early in the disease and remain relatively stable over time periods ranging from 6 months to 18 months (Abrahams, Leigh, & Goldstein, 2005; Irwin et al., 2007; Kilani et al., 2004; Schreiber et al., 2005; Strong et al., 1999). The few longitudinal studies in existence have been limited by relatively short follow-up periods, which may hamper validity of findings by increasing the likelihood of retest effects and failing to capture mild decline over the relatively short follow-up intervals (Irwin et al., 2007).

Emotional Lability in ALS

In addition to cognitive and physical impairments, ALS is associated with emotional lability (EL). EL, or pseudobulbar affect, is the involuntary occurrence of laughter or crying in the absence of a corresponding change in affect (Palmieri et al., 2009). The neuroanatomical basis of EL likely involves multiple regions of the brain: the cortex, brainstem motor nuclei, and a supranuclear center responsible for the integration of facial and respiratory movements involved in emotional expression (McCullagh, Moore, Gawel, & Feinstein, 1999). Evidence also suggests that alterations in the prefrontal cortex may play a role in EL. This is bolstered by the prefrontal cortex's known connections to structures and networks that control emotion regulation, as well as evidence of EL in patients who sustained focal strokes in this region (Morris, Robinson, & Raphael, 1993). Parvizi, Anderson, Martin, Damasio, and Damasio (2001) emphasized the involvement of cerebro-ponto-cerebellar pathways. Specifically, they suggested that EL results from disruptions in reciprocal pathways between the cerebellum and cortical and subcortical areas related to cognitive and

affective processing (e.g., ventromedial prefrontal cortex, anterior cingulate cortex, amygdala, and ventral striatum).

Studies conducted over the last decade have reported EL to occur in 19%-49% of patients with ALS (Palmieri et al., 2009; Richter, 2005). Although few studies have differentiated and reported specific symptomatology, Richter (2005) described a sample of 73 ALS patients, of whom 9.5% experienced pathological laughter, 12% pathological crying, and 27% both. EL has been associated with frontal lobe involvement (Averill, Kasarskis, & Segerstrom, 2007), disease progression (Palmieri et al., 2009), and bulbar symptomatology (Palmieri et al., 2009; Richter, 2005).

To date, only two studies have examined the relationship between EL and cognitive impairment in ALS. McCullagh et al. (1999) found a statistically significant difference in performance on the Wisconsin Card Sorting Test between 8 ALS patients with EL and 10 patients without. However, Palmieri et al. (2009) found no significant correlations between neuropsychological performance and EL in a sample of 41 patients with Motor Neuron Disease. Of note, theirs was a mixed sample including diagnoses of ALS, Primary Lateral Sclerosis, Progressive Bulbar Palsy, Progressive Muscular Atrophy, and Flail Arm Syndrome.

Depression in ALS

Prevalence estimates for depression in ALS have varied widely across studies, ranging from 0-100% of subjects reporting some level of depressive symptoms (Averill et al., 2007). In a study based on 1,707 patients with ALS, Miller et al. (2000) found that 31.3% of patients were experiencing depressive symptoms. The variability in reported prevalence is partially attributable to differing operational definitions and measures in assessing depression

(Taylor, Wicks, Leigh, & Goldstein, 2009), as well as symptoms that overlap in depression and ALS (e.g., fatigue and loss of energy). To date, only six studies have used DSM-IV criteria to diagnose clinically significant depression in patients with ALS (Bungener, Piquard, Pradat, Salachas, Meininger, & Lacomblez, 2005; Ganzini, Johnston, & Hoffman, 1999; Ganzini, Johnston, McFarland, Tolle, & Lee, 1998; Rabkin et al., 2005; Rabkin, Wagner, & Del Bene, 2000; Taylor et al., 2009). These six studies reported mood disorder diagnoses (e.g., Major Depressive Disorder or Dysthymic Disorder) in 0 to 11% of their samples. Studies based on self-report symptom inventories typically report higher rates (Averill et al., 2007) but describe mean symptom severity in the mild range (Grossman et al., 2007; Lulé et al., 2012; Rabkin et al., 2000). Additionally, only a few studies have included pertinent information regarding antidepressant medications, psychotherapy, or previous diagnoses of depression. Given the likely impact of these factors on reported symptomatology in these studies, previous results may underestimate the prevalence of depression or fail to consider the possibility that depressive symptoms in ALS are merely a recurrence of previous episodes of depression.

Contrary to once-prevalent belief, the incidence of depression in ALS is not solely attributable to increasing physical limitations. Most existing data is cross-sectional, but the majority of longitudinal data is not consistent with an increased rate of depression as death approached (Atassi, Cook, Pineda, Yerramilli-Rao, Pulley, & Cudkowicz, 2011; Averill et al., 2007; Rabkin et al., 2005). In fact, Rabkin et al. (2005) showed that depression was not correlated with disease severity or level of functional independence. Similarly, Hillemacher et al. (2004) found a negative correlation between depression severity and disease duration, suggesting that symptoms of depression may be more prevalent early in the disease, possibly

as part of an adjustment disorder secondary to the diagnosis. Hillemacher et al. (2004) also found that depressive symptom severity was associated with impaired swallowing and breathing, but not other functional impairments measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALS-FRS). On the other hand, Jelsone-Swain and colleagues (2012) found that increased Geriatric Depression Scale (GDS) scores were significantly associated with faster disease progression and limb dysfunction.

Jelsone-Swain and colleagues (2012) conducted the only existing study to examine the potential relationship of depressive symptoms on cognitive functioning in ALS. Although results of their MANCOVA showed a significant interaction effect between GDS scores and diagnosis group, the authors reported no significant main effect of depression or of the interaction between depression and diagnosis (i.e., ALS or control) on any single cognitive test. After follow-up analyses, they determined that different cognitive tests were associated with depressive symptoms in the ALS group as compared to the control group. Specifically, depressive symptoms in patients with ALS were associated with delayed verbal and nonverbal memory, semantic fluency, oral processing speed, visuospatial abilities, and confrontation naming, while controls with depressive symptoms performed more poorly on the MMSE, measures of verbal and nonverbal immediate recall, and phonemic fluency.

No previous studies were found that examined neuroanatomical correlates of depression in ALS; however, many investigators have linked depression to white and grey matter abnormalities in the prefrontal cortex, temporal lobe, hippocampus, and frontal-subcortical circuits in healthy adults and other neurological populations (Arnold et al., 2012; Lavretsky et al., 2007). Specifically, lower volumes have been reported in the orbitofrontal cortex, anterior cingulate (Drevets, Savitz, & Trimble, 2008), and gyrus rectus of patients

with geriatric depression. Similar areas of frontal lobe involvement have been reported in patients with depressive symptoms and other neurological disease (e.g., Huntington's disease, Parkinson's disease; Lavretsky et al., 2007). Given the overlap between these areas and the extramotor areas reported to be affected in the course of ALS, it seems warranted to investigate the relationship between cognitive impairment and depressive symptoms.

Apathy in ALS

Apathy is defined as "diminished motivation not attributable to decreased levels of consciousness, cognitive impairment, or emotional distress" (Lavretsky, Ballmaier, Pham, Toga, & Kumar, 2007) and is arguably the most common behavioral change associated with ALS. As with cognitive impairment in ALS, the involvement of extramotor areas may explain the presence of apathy in the disease. Woolley, Zhang, Schuff, Weiner, & Katz (2011) used diffusion tensor imaging (DTI) to quantify white matter changes associated with apathy in 16 participants with ALS. After accounting for age, gender, and functional impairment, the authors found apathy to be associated with significant reductions in the right anterior cingulum region, as well as the right superior longitudinal fasciculus and left frontal white matter. Given that apathy was not associated with depression, disease duration, or respiratory dysfunction, the authors suggested a biological basis for apathy. In addition, the common brain areas associated with apathy and cognitive impairment suggest a shared mechanism of impairment (Abrahams et al., 2004; Woolley et al., 2011).

The existing literature suggests that 30-60% of patients with ALS experience clinically significant apathy after disease onset (Grossman et al., 2007; Lillo, Mioshi, Zoing, Kiernan, & Hodges, 2011; Witgert et al., 2010). Diagnosis of apathy is difficult in the context of ALS and must be differentiated from declining physical abilities, depression, fatigue, and

respiratory dysfunction (Phukan et al., 2007; Woolley et al., 2011). However, several previous studies suggest that apathy exists independently of physical disease parameters (Grossman et al., 2007; Terada et al., 2011). Distinguishing apathy from depression can also be difficult, given symptom overlap (e.g., loss of interest) and relatively frequent comorbidity. However, a growing body of literature suggests that apathy is a behavioral syndrome that exists independently of depression in ALS (Grossman et al., 2007; Witgert et al., 2010) and in other neurodegenerative disorders (Havins, Massman, & Doody, 2013; Kirsch-Darrow, Marsiske, Okun, Bauer, & Bowers, 2011; Litvan, Mega, Cummings, & Fairbanks, 1996; Naarding, Janzing, Eling, van der Werf, & Kremer, 2009; Pluck & Brown, 2002; Tagariello, Girardi, & Amore, 2009; Zahodne & Tremont, 2012). This idea is supported by distinct symptomatology (e.g., sadness and hopelessness in depression vs. blunted emotional responsivity in apathy), varying rates of comorbidity across neurological disorders (Landes, Sperry, Strauss, & Geldmacher, 2001), and implied involvement of different neurotransmitters and distinct neuroanatomical regions and circuitry, as described above.

In addition to evidence that apathy is distinct, there is a growing body of literature to support the associations of apathy with impaired cognition and function in the context of many neurological disease processes (Chase, 2011). In patients with amnestic mild cognitive impairment (aMCI), Zahodne and Tremont (2012) found that both depression and apathy were associated with executive dysfunction, but only apathy was associated with functional impairment, independent of age, education and depressive symptoms. Importantly, at least two studies found that apathy predicted conversion from MCI to Alzheimer's dementia (AD), while depression did not (Chilovi et al., 2000; Palmer, et al., 2009). In fact, Palmer et al.

(2009) found that apathy was associated with a sevenfold risk of developing AD in cognitively impaired older adults. Even after conversion to dementia, apathy is associated with cognitive and functional deficits. Havins, Massman, and Doody (2013) showed that symptoms of apathy could be measured by the GDS and were associated with impaired verbal memory and basic functional abilities. On the other hand, symptoms of dysphoria were not associated with any cognitive or functional decline. In patients diagnosed with the behavioral variant of FTD, caregiver ratings of apathy were significantly related to patients' performances on measures of executive functioning and social cognition (i.e., theory of mind, empathy; Eslinger, Moore, Antani, Anderson, & Grossman, 2012). Similarly, apathy has been associated with cognitive and/or functional impairment in Parkinson's disease (Butterfield, Cimino, Oelke, Hauser, & Sanchez-Ramos, 2010; Dujardin, Sockeel, Delliaux, Destée, & Defebvre, 2009; Pluck & Brown, 2014; Varanese, Perfetti, Chilardi, & Di Rocco, 2011), progressive supranuclear palsy (Litvan, et al., 1996), stroke (Jorge, Starkstein, & Robinson, 2010), and traumatic brain injury (Andersson & Bergedalen, 2002). Across patient populations, research shows that apathy is also associated with poorer general health, reduced treatment compliance, reduced quality of life, and increased caregiver stress and burden (Chase, 2011; vanReekum, Stuss, & Ostrander, 2005). Importantly, the relationship between apathy and these patient factors may actually be under-reported in the literature. Given the number of depression symptom inventories that also assess symptoms of apathy, it may be that studies unintentionally inflate the relationship of depression to impairment in neurological disease, which would be more accurately attributed to apathy.

Few studies have investigated the relationship between apathy and cognitive impairment in ALS (Girardi et al., 2011; Grossman et al., 2007; Witgert et al., 2010). Witgert

et al. used k clustering and ANOVAs to investigate the relationship among three levels of cognitive impairment and behavioral impairment as measured by the Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2001). Results showed that cognitive impairment was associated with overall behavioral impairment, but only significantly associated with the apathy subscale of the FrSBe. Additional correlational analyses revealed that total apathy scores were significantly associated with impairments in semantic fluency, attention, mental flexibility, and a timed measure of visuospatial construction. Grossman et al. (2007) found that FrSBe apathy scores predicted performance on measures of verbal fluency. Of note, they combined results from two small samples using different verbal fluency measures, excluded subjects with Major Depressive Disorder (MDD), and did not control for relevant disease severity variables.

Study Purpose and Hypotheses

The presence of cognitive impairment in some patients with ALS is now a known fact. However, the predictors of cognitive impairment in ALS are not fully understood. As noted above, data from neuroimaging studies demonstrates that cognitive dysfunction is associated with extramotor areas of the brain affected by the disease process. However, the overlap in affected brain structures in ALS and apathy, as well as the associations between cognitive impairment and apathy in other neurological disorders, suggest that apathy may play a role in cognitive impairment above and beyond the disease process itself. In light of the additional hardships experienced by patients with apathy as outlined above, it is critical to identify those patients suffering from cognitive impairment and/or apathy and address these and comorbid issues appropriately. Given the prevalence of apathy, depression, and EL in ALS, the symptom overlap among them, and the potential overlap in their neuroanatomical

basis in ALS (e.g., prefrontal cortex, anterior cingulate cortex), it is important to consider all three syndromes to provide a clear and complete picture.

To date, no study has systematically examined cognitive profiles associated with apathy, depression, and EL in a sample of patients with ALS. In addition to introducing this type of investigation, we intended to improve upon previous studies' methodology by including the following elements: 1) a large sample size, 2) a diagnostically homogeneous sample of patients with ALS by validated criteria, 3) DSM-IV-*TR* diagnosis of Mood and Adjustment Disorders (MAD) rather than self-report symptom indices, 4) information about patients' current psychotropic medications and previous psychiatric diagnoses, and 5) well-known and validated measures of neuropsychological functioning.

Specific hypotheses were:

1. In light of reports by previous studies, I expected at least 30% of the sample to endorse clinically significant apathy (as defined by T-scores greater than 65 on the FrSBe).
2. Based on the limited literature in ALS and substantial documentation in other neurological populations, I expected higher apathy scores to predict worse performance on measures of rote attention, verbal fluency, psychomotor speed, working memory, and mental flexibility.
3. After accounting for apathy, DSM-IV diagnosis of mood disorder would not predict performance on any neuropsychological measure.
4. After accounting for apathy, the presence of emotional lability would not predict performance on any neuropsychological measure.

Methods

Participants

Participants were consecutive referrals to the neurology service of The Houston Methodist Hospital MDA-ALS clinic from 2009-2013. All patients met El Escorial World Federation of Neurology diagnostic criteria for probable or definite ALS (Brooks, 1994; Brooks et al., 2000), eliminating those with possible ALS. Patients with probable ALS were included, given that diagnostic criteria for probable and definite ALS are very similar (upper and lower motor neuron signs in two regions for probable and in three regions for definite) and patients with either diagnosis receive the same treatment. Independent t-tests and Fisher's exact tests were conducted to compare the patients with definite ALS to those with probable ALS on all relevant demographic, clinical, and cognitive variables. There were no statistically significant differences between the groups on any variable, with the exception of disease duration. Patients with a history of other neurologic conditions affecting cognition (e.g., stroke, traumatic brain injury), serious mental illness (e.g., schizophrenia), or whose initial diagnosis of ALS was later changed to another diagnosis (e.g., multifocal motor neuropathy) were excluded. Although we originally planned to include patients with ALS-FTD in our sample, they were ultimately excluded based on low sample size (n = 8) and concern that violating diagnostic homogeneity would limit generalizability of results. In order to ensure that participants were able to appropriately respond to self-report questionnaires, any patient scoring > 2 SD below the age-based mean on the Wide Range Achievement Test-R Reading Subtest (WRAT Reading; Jastak & Wilkinson, 1984) was excluded. Participants without complete FrSBe data were not included in the regression analyses. Due to time constraints and physical limitations, some patients were unable to

complete all measures in the neuropsychological battery. This protocol was approved by the institutional review boards of The Houston Methodist Hospital and the University of Houston.

As shown in Table 2, the final sample included 161 patients (57.8% male) with a mean age of 61.0 years (SD = 11.1) and a mean educational level of 14.5 years (SD = 2.6). MMSE and WRAT-4 Reading scores suggested that patients in the final sample were within normal limits with respect to their overall cognitive functioning and level of premorbid verbal intellectual functioning. Of the 161 patients included, 152 patients had a diagnosis of definite ALS, and the remaining 9 were diagnosed with probable ALS. Most patients (71%) had limb onset (the remaining 29% had bulbar onset). The mean score on the Appel ALS Rating Scale was 68.3 (SD = 23), suggesting total disease severity in the mild-to-moderately impaired range. The mean duration between the onset of symptoms and disease diagnosis was 16.4 months (SD = 15.3). Disease duration ("Months into Disease") was defined as the time since the patient reported experiencing the first symptom of the disease. A subset of those patients (N = 117) had complete FrSBe data and was included in the regression analyses (see Table 3 for demographic and clinical information on this subsample).

Measures

All participants underwent comprehensive neuropsychological evaluation, including measures of cognition, mood, and behavior. All raw scores on neuropsychological measures were converted to z-scores, based on age-, gender-, race-, and education-based normative data, when possible. Based on this study's hypotheses and the existing literature, the following measures were included in the analyses:

Premorbid Functioning

The Wide Range Achievement Test-R Reading Subtest (WRAT Reading; Jastak & Wilkinson, 1984) is a single-word reading test used to assess reading level and is often used as a measure of premorbid functioning. Words increase in difficulty as the list progresses (e.g., from "in" to "terpsichorean"). Subjects are asked to read the words aloud to the examiner, one at a time. Points are given for correct pronunciation. Raw scores range from 0 to 70, and both age-based standard scores and grade-equivalent scores are provided (the former were utilized in this study).

General Mental Status

The MMSE (Folstein, Folstein & McHugh, 1975) is a frequently-used measure to screen for cognitive impairment. The MMSE measures orientation to time and place, attention and calculation, immediate and delayed recall of three words, naming, repetition, comprehension, reading, writing, and visual construction. The maximum score is 30 points.

Attention

WAIS-III Digit Span Forward (DSF; Wechsler, 1997) is a measure of rote auditory attention. The examinee is asked to repeat series of digits presented aurally. The length of the digit series increases over trials.

Processing Speed

Trail Making Test part A (TMTA; Army Individual Test Battery, 1944) is a visuomotor measure of processing speed that requires a subject drawing lines to connect numbers 1 through 25 placed randomly on a single page. Scores are based on the time in seconds it takes the subject to complete the task.

Verbal Fluency

The FAS test (Spreen & Benton, 1977) was designed to assess phonemic fluency. It is also a measure of executive function that requires initiation, strategy, and mental flexibility. An examinee is asked to orally produce as many words as possible beginning with the letters F, A, and S. One minute is allotted per letter.

Semantic fluency (Animals; Goodglass & Kaplan, 1983) was assessed by asking subjects to name as many different kinds of animals as possible in one minute.

Memory

The Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict, Schretlen, Groninger, & Brandt, 1998) is a measure of verbal learning and memory. The examiner reads a list of 12 nouns that each belong to one of 3 categories (i.e., animals, precious stones, or dwellings). The subject is asked to recall as many words as possible. This is repeated over two additional trials. After a 25-minute delay, there is a delayed free recall trial, followed by a yes/no recognition test. The sample size for this measure was significantly smaller than most of the other cognitive measures included in this study. This was due to the fact that the preferred verbal memory measure in the clinical battery was changed during the period of data collection.

Other Executive Functions

Trail Making Test part B (TMTB; Army Individual Test Battery, 1944) is a visuomotor measure of divided attention, multitasking, and cognitive flexibility. The subject is asked to draw lines connecting numbers 1 to 13 and letters A to L, in order. The subject must alternate between numbers and letters (e.g., 1-A-2-B-3-C, etc.). Scores are based on the time in seconds it takes the subject to complete the task.

WAIS-III Digit Span Backwards (DSB; Wechsler, 1997) measures auditory working memory. The examinee is asked to listen to a series of digits and repeat them to the examiner in reverse order. The length of the digit series increases from 2 to 9 over trials.

The Wisconsin Card Sorting Test (WCST; Kongs, Thompson, Iverson, & Heaton, 2000) is a measure of hypothesis testing and problem-solving, set shifting, and perseveration. An examinee is asked to "match" a set of 64 cards with colored shapes to four key cards, but is not instructed on how to make a match. Matching options include color (i.e., red, green, yellow, blue), form (i.e., triangle, star, cross, circle), and number (i.e., 1, 2, 3, or 4 elements on the card). The examiner provides feedback after every match. After ten correct matches, the examiner changes the sorting principle (e.g., from color to form) in a predetermined order without informing the patient. This measure had a smaller sample size than many of the other measures included in the analyses, as WCST was often eliminated from the clinical battery if a patient's functioning was otherwise within normal limits.

Assessment of Depression

The Mini International Neuropsychiatric Inventory (MINI; Sheehan et al., 1998) is a short, semi-structured diagnostic interview, designed to assess the presence of 17 DSM-IV Axis I diagnoses. Diagnoses are made by patient self-report and examiner's clinical judgment. The MINI uses branching tree logic and two to four screening questions per disorder. Additional symptoms are asked about only if the screening questions are positively endorsed. This instrument has sound psychometric properties, including satisfactory test-retest reliability, inter-rater reliability, convergent validity, sensitivity, and specificity (Lecrubier et al., 1997; Sheehan et al., 1997; Sheehan et al., 1998). For the purpose of this study, the MINI MDD module was administered by the examiner. Additional diagnoses of

Dysthymic Disorder, Adjustment Disorder with Depressed Mood, and Adjustment Disorder with Mixed Anxiety and Depressed Mood were made by the examiner based on clinical interview and DSM-IV-*TR* criteria. All four additional diagnoses were included in the analyses, as all four represent clinically significant depressive symptoms that may affect performance on cognitive measures.

The Beck Depression Inventory-II (BDI-II) is a multiple choice, self-report questionnaire that measures the presence and severity of common depressive symptoms. The scale includes 21 items ranging in value from 0 to 3 points, yielding a maximum total score of 63. Scores less than 14 are considered to be indicative of minimal depression, total scores 14-19 to be mild depression, scores 20-28 to be moderate depression, and scores greater than or equal to 29 represent severe depression.

Assessment of Apathy

The FrSBe (Grace & Malloy, 2001) is a 46-item questionnaire measuring pre-illness and current behavior in three dimensions: apathy, disinhibition, and executive dysfunction. The apathy subscale (14 items) assesses initiation, spontaneity, drive, persistence, energy, interest, concern about self-care, psychomotor retardation and blunted affect. A standardized T-score greater than 65 is considered to be indicative of clinically significant apathy. Reliability for the total score and post-illness scores has been reported at 0.95. The scale's creators have also demonstrated excellent construct validity (Grace, Stout, & Malloy, 1999; Stout, Ready, Grace, Malloy, & Paulsen, 2003), and the apathy subscale has good discriminant validity with regard to depression (Clarke, Ko, Kuhl, van Reekum, Salvador, & Marin, 2011). Specifically, previous authors have reported weak-to-moderate correlations (ranging from .13 to .38) and/or statistically insignificant relationships between the FrSBe

apathy scale and well-validated measures of depression in patients with ALS (with the BDI-II; Grossman et al., 2007) and other neurologic diseases (Cahn-Weiner, Grace, Ott, Fernandez, & Friedman, 2002; Grace & Malloy, 2001; Lane-Brown & Tate, 2009; Norton, Malloy, & Salloway, 2001). For this sample, the caregiver form was used.

Assessment of Emotional Lability

Emotional lability was defined as mood-incongruent, uncontrollable laughing and/or crying spells that affected patients' functioning. Emotional lability was scored dichotomously, based on the attending neurologist's examination, information gathered from the patient and family members during the clinical neuropsychological interview, and behavioral observations during neuropsychological assessment.

Disease Severity

The Appel ALS Rating Scale (Appel, Stewart, Smith, & Appel, 1987) provides a quantitative estimate of clinical status and disease progression in ALS patients, measuring function in the following domains: swallowing, speech, respiratory function, and strength and function of upper and lower extremity musculature. Scores are produced for five scales: Bulbar (speech and swallowing), Respiratory, Muscle Strength (upper and lower extremities), Muscle Function-Lower Extremities, and Muscle Function-Upper Extremities (UE Function). Each scale is scored individually, with scores ranging from 6 (no dysfunction) to 30-36 (maximal dysfunction). Total scale scores range from 30 to 164. For the purposes of this study, Bulbar total scores were used in regression models predicting neuropsychological measures that require verbal output. Muscle Function-Upper Extremities total scores were used in regression models predicting neuropsychological measures that require manual motor output.

Table 2. Demographic and Clinical Information for Final Sample (N = 161)

Characteristic	Mean (SD)	Number	Percentage	Range
Age	61.0 (11.1)			32.2-86.6
Education	14.5 (2.6)			8-20
Sex				
Female		68	42.2	
Male		93	57.8	
El Escorial Diagnosis				
Definite ALS		152	94.4	
Probable ALS		9	5.6	
Clinical Picture				
Limb Onset		115	71.4	
Bulbar Onset		46	28.6	
Appel ALS Rating Scale				
Total Score	68.3 (23.0)			36-145
Bulbar Score	11.7 (6.1)			6-30
Upper Extremity Score	14.6 (6.7)			6-33
Months Into Disease	16.4 (15.3)			3-120
MMSE Total Score	28.8 (1.4)			24-30
WRAT-4 Reading Standard Score	101.9 (9.3)			79-120

Table 3. Demographic and Clinical Information for Regression Sample (N = 117)

Characteristic	Mean (SD)	Number	Percentage	Range
Age	60.5 (11.0)			33.2-86.6
Education	14.6 (2.6)			8-20
Sex				
Female		47	40.2	
Male		70	59.8	
El Escorial Diagnosis				
Definite ALS		110	94.0	
Probable ALS		7	6.0	
Clinical Picture				
Limb Onset		84	71.8	
Bulbar Onset		33	28.2	
Appel ALS Rating Scale				
Total Score	68.5 (23.2)			36-143
Bulbar Score	11.6 (6.1)			6-30
Upper Extremity Score	14.7 (6.9)			6-33
Months Into Disease	16.0 (13.5)			3-84
MMSE Total Score	28.8 (1.5)			24-30
WRAT-4 Reading Standard Score	102.1 (8.9)			79-120

Analyses

Descriptive information was generated to delineate the prevalence of apathy, mood and adjustment disorders (MAD), and EL. Descriptive information was also generated for all

cognitive variables, with percentages of impairment (defined as > 1.5 SD below the mean) for all measures. T-tests were used to compare pre- and post-illness apathy scores, as well as to compare change scores for all three subtests of the FrSBe. Pearson correlations were computed to examine the relationship between FrSBe subscales, between FrSBe subscales and cognitive measures, and between neuropsychiatric disorders and cognitive measures. Phi coefficients were calculated to explore the relationships between the dichotomous neuropsychiatric variables. In order to compare prevalence rates of neuropsychiatric disorders between those patients with spinal or bulbar onset, Fisher's exact test was used.

Hierarchical multiple regression analyses were used to predict continuous scores on neuropsychological variables from dichotomous measures of apathy, depression, and EL. In order to control for physical symptoms of the disease and their potential contribution to symptoms of depression and cognitive impairment, Appel ALS Bulbar or UE Function subscale scores were entered into the first block. Apathy, MAD, and EL were entered together into the second block. If any of the neurobehavioral variables emerged as an independent predictor in that second block, an additional regression analysis was conducted in order to determine the unique contribution of the independent predictor over and above the other independent variables. The same analyses were repeated with apathy, DSM-IV-*TR* Mood Disorders, and EL, excluding adjustment disorders.

In light of the limited results found with the dichotomous variables, analyses were repeated with continuous variables, based on BDI-II and FrSBe post-illness apathy scale T-scores.

Before beginning these analyses, the data were inspected for outliers. With respect to the cognitive variables, only HVLT-R, TMTB, and WCST had skewness values that

warranted further inspection. For HVLT-R Delayed Recall, one extreme value was changed to the next lowest value (-5.00). For TMTB, five extremely low values were changed to the lowest value continuous with the other scores (-5.00). Lastly, for WCST perseverative responses, one high value was changed to the next highest value (43). Then, the skewness and kurtosis of each of these variables was examined and found to be within suggested value ranges (between -1 and 1). One subject was eliminated on the basis of age (27 years). All statistical analyses were conducted using SPSS Statistics Version 22.

Results

Hypothesis 1

Of the 117 patients with complete FrSBe data, 38 patients (32.5%) were experiencing clinically significant apathy. The mean apathy subscale T-score for the sample was 58.9 (SD = 16.9). Paired samples *t*-tests were performed to compare pre-illness and current apathy scores. Mean pre-illness and post-illness apathy T-scores were 49.3 and 58.9, respectively, $t(116) = -8.89$, $p < .001$. On average, apathy T-scores increased by 9.5 points (nearly one standard deviation) between the two time points rated by caregivers, and 29 patients (18%) whose scores were not clinically significant before illness onset had scores in the clinically significant range at the time of their evaluation. To investigate differences between FrSBe subscale change scores, dependent samples *t*-tests were performed. Apathy change scores were significantly greater than change scores on the Disinhibition and Executive Dysfunction subscales, $t(116) = 5.21$, $p < .001$, and $t(116) = 7.12$, $p < .001$, respectively. Disinhibition change scores were significantly greater than Executive Dysfunction change scores, $t(116) = 2.84$, $p = .005$.

Apathy scores were significantly and moderately correlated with scores on the other FrSBe subscales, and change scores from all three subscales were significantly related (all $p < .001$). See Table 4 for subscale intercorrelation information and Table 5 for correlations between FrSBe subscales and cognitive measures of interest.

Table 4. Correlations between FrSBe Subscales and Change Scores

	Post-Illness Apathy	Post-Illness Disinhibition	Post-Illness ED	Apathy Change	Disinhibition Change	ED Change
Post-Illness Apathy	--	.56**	.67**			
Post-Illness Disinhibition		--	.82**			
Post-Illness ED			--			
Apathy Change				--	.31**	.39**
Disinhibition Change					--	.63**
ED Change						--

Note. ED = Executive Dysfunction
* $p < .05$; ** $p < .01$

Table 5. Correlations between FrSBe Subscales and Cognitive Measures

Variable	**Apathy**	**Disinhibition**	**ED**
DSF	-.15	-.09	-.02
DSB	-.16	-.14	-.09
HVLT-R Immediate	-.09	-.24	-.25*
HVLT-R Delayed	-.03	-.11	-.14
Animals	-.16	-.16	-.25*
FAS	-.25**	-.24*	-.28**
TMTA	-.12	-.29**	-.21*
TMTB	-.32**	-.28**	-.32**
WCST PRs (raw)	.21	.17	.17

Note. All FrSBe subscales values are for Post-Illness T-scores. ED = Executive Dysfunction
PR = perseverative responses; * $p < .05$.** $p < .01$

Thirty patients (18.6%) met criteria for DSM-IV-*TR* diagnosis of a MAD. Specifically, 16 patients endorsed symptoms consistent with a mood disorder (i.e., Major Depressive Disorder or Dysthymic Disorder), and 14 patients endorsed symptoms consistent with an adjustment disorder. See Tables 6 and 7 for more information regarding specific diagnoses. Of those 13 patients who met criteria for MDD, all reported previous mood disorder diagnoses, and all but two were prescribed an antidepressant medication. Two of three participants diagnosed with Dysthymic Disorder had previous diagnoses and current

antidepressant prescriptions. In the final sample, 101 participants had complete BDI-II data. Their mean score was 8.9 (SD = 6.8), and only 20 patients (19.8%) scored above the cut-off for clinically significant depressive symptoms. Of those, 13 patients scored in the mildly depressed range, 6 scored in the moderate range, and 1 scored in the severely depressed range. Of those 131 patients who did not meet criteria for a MAD, 37 (28.2%) had previous depression diagnoses and 25 (19.1%) were taking an antidepressant medication.

Table 6. Descriptive Information for Neuropsychiatric Variables for Full Sample

Measure	N	Mean (SD)	Number	Percentage	Range
MINI	**161**				
No Disorder			**131**	**81.4**	
MAD			**30**	**18.6**	
Mood Disorder			**16**	**9.9**	
MDD			13	8.1	
Dysthymic Disorder			3	1.8	
Adjustment Disorder			**14**	**8.7**	
Adjustment Disorder with Depressed Mood			10	6.2	
Adjustment Disorder with Mixed Anxiety and Depressed Mood			4	2.5	
EL	**161**				
Not Clinically Significant			121	75.2	
Clinically Significant			40	24.8	
MAD and EL	**161**		**13**	**8.1**	
Mood Disorder and EL			8	5.0	
Adjustment Disorder and EL			5	3.1	

Forty patients (approximately 25%) were experiencing EL at the time of their neuropsychological evaluation, and half of these patients had been prescribed Nuedexta (typically initiated 1-2 days prior to their evaluation). Prevalence rates did not differ by site of disease onset (limb vs. bulbar; see Table 8).

In the interest of examining comorbidity of these neuropsychiatric disorders in ALS, additional descriptive analyses were conducted. Of those 117 patients with complete FrSBe data, 13 patients had clinically significant apathy and diagnosis of a MAD. Fourteen patients had comorbid apathy and EL. Thirteen patients met criteria for a MAD and EL. Only 6

patients had clinically significant apathy, EL, and met criteria for a MAD. When only Mood Disorders were considered, 20 of the 117 patients were experiencing two or more neuropsychiatric disorders. With the inclusion of Adjustment Disorder diagnoses, 26 patients (22.2%) were experiencing two or more clinically significant neuropsychiatric disorders. See Tables 6, 7, and 9 for additional information about comorbidity.

Table 7. Descriptive Information for Neuropsychiatric Variables for Regression Sample

Measure	N	Mean (SD)	Number	Percentage	Range
FrSBe Apathy (T-score)	**117**	**58.9 (16.9)**			**33-107**
Normal range (≤ 65)			79	67.5	
Significant Apathy (> 65)			38	32.5	
Apathy and MAD	**117**		**13**	**11.1**	
Apathy and Mood Disorder			7	6.0	
Apathy and Adjustment Disorder			6	5.1	
Apathy and EL	**117**		**14**	**12.0**	
MAD and EL	**117**		**11**	**9.4**	
Mood Disorder and EL			7	6.0	
Adjustment Disorder and EL			4	3.4	
Apathy, MAD, and EL	**117**		**6**	**5.1**	
Apathy, Mood Disorder, and EL			4	3.4	
Apathy, Adjustment Disorder, and EL			2	1.7	
BDI	**101**	**8.9 (6.8)**			**1-44**
Normal Range (< 14)			81	80.2	
Depressed Range (≥ 14)			20	19.8	

Table 8. Prevalence Rates of Neuropsychiatric Disorders by ALS Onset

	N	MDD N (%)	Dysthymic D/O N (%)	Adjustment D/O N (%)	EL N (%)	Apathy N (%)
Spinal Onset	84	6 (7.1)	3 (3.6)	8 (9.5)	20 (23.8)	28 (33.3)
Bulbar Onset	33	4 (12.1)	0	2 (6.1)	12 (36.4)	10 (30.3)
Fishers Exact Test		.47	.56	.72	.18	.83

Table 9. Number of Patients Meeting Criteria for Comorbid Neuropsychiatric Diagnoses

	N	No Diagnosis N (%)	1 Diagnosis N (%)	2 Diagnoses N (%)	3 Diagnoses N (%)
Mood Disorders Only	117	58 (49.6)	39 (33.3)	16 (13.7)	4 (3.4)
Mood and Adjustment Disorders	117	56 (47.9)	35 (29.9)	20 (17.1)	6 (5.1)

Lastly, Phi coefficients were calculated to explore the relationships between the neuropsychiatric variables of interest. As shown in Table 10, apathy had a weak, but statistically significant positive relationship with adjustment disorders, but was not

significantly associated with mood disorders or EL. Mood disorders, but not adjustment disorders, were significantly correlated with EL.

Table 10. Phi Coefficient Matrix for Neuropsychiatric Variables

	Apathy	MAD	Mood Disorder	Adjustment Disorder	EL
Apathy	--	.25**	.16	.18*	.16
MAD		--			.18*
Mood Disorder			--		.19*
Adjustment Disorder				--	.08
EL					--

* $p < .05$; ** $p < .01$

Hypotheses 2, 3, and 4

See Table 11 for descriptive information on the cognitive variables. The most frequently impaired cognitive measures were HVLT-R Immediate and Delayed Recall (38.1% and 39.7% of the sample, respectively), while the least frequently impaired were DSF and DSB (0.9% and 2.8%, respectively). Given the unexpected difference in impairment rates for verbal memory and phonemic fluency, additional analyses were conducted in an attempt to clarify these findings. The rate of FAS impairment was similar in the 63 participants who had data for HVLT-R (9.5%). In the 49 patients who were administered FAS, but not the HVLT-R, 18.4% of patients' FAS scores were impaired. Independent t-tests, Phi coefficients, and Fisher's exact tests were conducted to compare the patients given both HVLT-R and FAS to those patients administered only FAS on all relevant demographic and clinical variables, including EL, MAD, and apathy. There were no statistically significant differences between the groups on any variable.

Pearson correlations were conducted to inspect the relationships between the neuropsychiatric variables and scores on the cognitive measures. Increased apathy was associated with poorer performances on phonemic fluency and TMTB (r = -.23, p = .008 and r = -.33, p = .001, respectively). Mood disorders were significantly and negatively correlated

only with DSF (r = -.22, p < .010). MADs were significantly and negatively correlated with DSF, as well as DSB (r = -.16, p = .049) and phonemic fluency (r = -.19, p = .025). EL was significantly and negatively correlated with phonemic fluency (r = -.25, p = .005) and TMTA (r = -.25, p = .007).

Table 11. Descriptive Information for Cognitive Variables

Measure	N	Mean (SD)	Range	% Impaired*
DSF	107	-.04 (0.81)	-1.77-1.92	0.9
DSB	106	-.01 (0.85)	-1.91-2.26	2.8
TMTA	98	.03 (1.23)	-3.97-2.11	11.2
TMTB	96	-.66 (1.79)	-5.00-2.34	29.2
HVLT-R Immediate Recall	63	-1.15 (1.33)	-4.23-1.34	38.1
HVLT-R Delayed Recall	63	-1.08 (1.38)	-5.00-1.16	39.7
Animals	106	-.05 (1.20)	-3.14-4.33	10.4
FAS	112	-.51 (0.93)	-2.47-1.90	12.5
WCST Perseverative Responses (raw score)	67	13.09 (8.73)	3.00-43.00	

*Impairment defined as ≥ -1.67z (Strong et al., 2009)

The two disease severity variables of interest were significantly related to almost all of the cognitive variables. AALS Bulbar subtotal scores were negatively correlated with scores on DSB, immediate and delayed verbal memory, and phonemic and semantic fluency. AALS UE Function scores were associated with worse performances on TMTA and TMTB. See Table 12 for a full correlation matrix for all relevant variables.

Table 12. Correlation Matrix, Neuropsychiatric and Cognitive Variables

Variable	Apathy[a]	MAD[b]	Mood Disorder[c]	EL[d]	AALS Bulbar	AALS UE Function
AALS Bulbar	.18*	.03	.02	.35**	--	.23**
AALS UE Function	.24*	.13	.13	.17*	.23**	--
DSF	-.15	-.19*	-.22**	-.14	-.14	
DSB	-.09	-.16*	-.15	-.08	-.23**	
HVLT-R Immediate	.04	.08	.10	-.05	-.24*	
HVLT-R Delayed	.09	.09	.12	-.04	-.23*	
Animals	-.11	-.12	-.05	-.14	-.27**	
FAS	-.23**	-.19*	-.01	-.25**	-.16*	
TMTA	-.14	-.03	< .01	-.25**		-.39**
TMTB	-.33**	-.09	-.07	-.09		-.41**
WCST PRs	.12	-.05	-.05	.05		.20

[a]0 = T < 65, 1 = T ≥ 65; [b]0 = No DSM-IV-*TR* Mood or Adjustment Disorder, 1 = Mood or Adjustment Disorder; [c]0 = No DSM-IV-*TR* Mood disorder, 1 = MDD or Dysthymic Disorder; [d]0 = Absence of emotional lability, 1 = Emotional lability; WCST PRs = WCST perseverative responses
* p < .05.** p < .01

In order to determine whether apathy could predict performance on neuropsychological measures, hierarchical regression analyses were performed. As described above, for each of these analyses, disease severity was entered into the first block, and apathy, MAD, and EL were entered together into the second block. Please see Appendix 2 for complete regression results.

For DSF, Bulbar scores in block 1 accounted for 6.3% of the total variance, and the model was not significant, F (4,102) = 1.73, p = .15. The addition of the neurobehavioral variables did not contribute a significant amount of variance (R^2 change = .04, p = .196), and the total model was not significant. In the full model, none of the predictors showed significant independent contributions to scores on DSF; thus, additional regressions were not conducted.

For DSB, Bulbar scores in block 1 accounted for 5.2% of variance in DSB scores, and the model was significant, F(1,104) = 5.71, p = .019. The addition of the neurobehavioral variables did not significantly increase the variance accounted for (R^2 change = .03, p = .440), and the full model was not statistically significant (p = .086). In the full model, only Bulbar scores independently predicted scores on DSB (β = -.24, p = .025).

Bulbar scores in block 1 accounted for 5.7% of variance in HVLT immediate recall scores, and the model approached significance, F(1,61) = 3.68, p = .060. The addition of the neurobehavioral variables did not significantly increase the variance accounted for (R^2 change = .01, p = .94), and the full model was not statistically significant (p = .43). In the full model, none of the predictors showed significant independent contributions to HVLT-R scores.

Similarly, Bulbar scores in block 1 accounted for 5.3% of variance in HVLT-R delayed recall scores, and the model approached significance, $F(1,61) = 3.42$, $p = .069$. The addition of the neurobehavioral variables did not significantly increase the variance accounted for (R^2 change = .01, $p = .86$), and the full model was not statistically significant ($p = .41$). None of the predictors made significant independent contributions to HVLT-R delayed recall scores.

Bulbar scores in block 1 accounted for 7.4% of variance in semantic fluency scores, and the model was statistically significant, $F(1,104) = 8.31$, $p = .005$. The addition of the neurobehavioral variables did not significantly increase the variance accounted for (R^2 change = .01, $p = .78$), and the full model only approached significance, $F(4,101) = 2.31$, $p = .063$. With all variables in the model, only Bulbar scores independently predicted semantic fluency scores ($\beta = -.25$, $p = .017$).

For phonemic fluency, Bulbar scores in block 1 accounted for 2.5% of variance in the scores, and the model was not statistically significant, $F(1,110) = 2.82$, $p = .096$. The addition of the neurobehavioral variables did significantly increase the variance accounted for (R^2 change = .08, $p = .026$), and the full model was statistically significant, $F(4,107) = 3.16$, $p = .017$. However, none of the predictors in the full model made significant independent contributions to phonemic fluency scores.

In block 1, UE Function accounted for 14.9% of variance in TMTA scores, and the model was statistically significant, $F(1,94) = 16.49$, $p < .001$. The addition of the neurobehavioral variables did not significantly increase the variance accounted for (R^2 change = .04, $p = .27$), but the full model remained significant, $F(4,91) = 5.18$, $p = .001$.

With all variables in the model, only UE Function scores independently predicted fluency scores (β = -.35, p = .001), but EL approached significance (β = -.19, p = .062).

In block 1, UE Function accounted for 17.1% of variance in TMTB scores, and the model was statistically significant, $F(1,92) = 19.02$, $p < .001$ (see Table 13). In block 2, the addition of the neurobehavioral variables did not significantly increase the variance accounted for (R^2 change = .06, p = .083), but the full model remained significant, $F(4,89) = 6.68$, $p < .001$. In the final model, both UE Function scores and apathy independently predicted TMTB scores (β = -.37, $p < .001$ and β = -.26, p = .010, respectively). An additional 3-step regression was conducted, with UE Function in the first block, Depression and EL in the second block, and apathy in the third block. Apathy contributed an additional 5.9% of variance to the model, over and above the contributions of UE Function, depression, and EL (p = .010).

Table 13. Results of Multiple Hierarchical Regressions Predicting TMTB scores

	Step 1			Step 2			Step 3		
Variable	B	SE	β	B	SE	β	B	SE	β
TMTB									
AALS UE Function	-.14	.03	-.41**	-.14	.03	-.41**	-.12	.03	-.40**
Depression				-.05	.44	-.01	.27	.45	.06
EL				.01	.40	.00	.11	.39	.03
Apathy							-1.01	.39	-.26**
R^2			.17			.17			.23
F			19.02**			6.21**			6.68**
ΔR^2			.17			.00			.06
ΔF			19.02**			.01			6.87**

* $p < .05$.** $p < .01$

Lastly, UE Function in block 1 accounted for 4% of the variance in WCST perseverative responses, and the model was not statistically significant, $F(1,64) = 2.69$, p = .11. The addition of the neurobehavioral variables did not significantly increase the variance accounted for (R^2 change = .02, p = .74), and the full model was not significant, $F(4,61) = 0.97$, p = .43. None of the predictors made significant independent contributions to the

model. In an attempt to further isolate clinically significant depression, the analyses were repeated including only DSM-IV-*TR* mood disorders (i.e., excluded adjustment disorders). Results were not significantly different for any of the models.

These analyses were repeated with continuous measures of depression (BDI-II) and apathy (FrSBe apathy T-scores). Results for phonemic fluency, TMTB, and WCST perseverative responses were slightly different than analyses conducted with dichotomous predictors. Unlike results from the previous analyses, the addition of the continuous neuropsychiatric variables did not contribute a significant amount of variance in phonemic fluency scores (R^2 change = .06, p = .13), and the full model was not statistically significant $F(4,94) = 1.88$, p = .12. Like analyses with dichotomous variables, none of the predictors made independent contributions to phonemic fluency scores. For TMTB, the addition of the continuous neurobehavioral variables in block 2 did not significantly increase the variance accounted for (R^2 change = .07, p = .061), but, again, the full model remained significant, $F(4,79) = 6.48$, $p < .001$. In the final model, only UE Function scores independently predicted TMTB scores ($\beta = -.12$, p = .001), and apathy was no longer a significant independent predictor. For WCST perseverative responses, although the models remained statistically insignificant, depression and apathy both emerged as independent predictors in the final model ($\beta = -.33$, p =.049 and $\beta = .35$, p = .030, respectively). Given that the direction of the relationship between WCST perseverative responses and depression suggests that less severe depressive symptomatology is associated with greater number of perseverative responses, additional analyses were not conducted with depression. An additional 3-step regression was conducted with UE Function in the first block, Depression and EL in the second block, and apathy in the third block. Apathy contributed an additional

7.8% of variance to the model, over and above the contributions of UE Function, depression, and EL (p = .030). Results for DSF, DSB, HVLT-R Immediate Recall, HVLT-R Delayed Recall, semantic fluency, and TMTA were not different from the original analyses.

Discussion

Hypothesis 1 was supported by the data. Approximately 33% of patients in this sample were experiencing clinically significant post-illness symptoms of apathy, consistent with previously reported prevalence rates (Witgert et al., 2010). Importantly, 76% of those patients with clinically significant apathy did not have clinically significant pre-illness apathy scores. In addition, apathy scores increased, on average, by almost one standard deviation between pre-illness and post-illness ratings. Apathy scores increased significantly more than the disinhibition and executive dysfunction subscales of the FrSBe. Together, results suggested that ALS was associated with an increased likelihood of developing symptoms of apathy.

Approximately 10% of the sample met DSM-IV-*TR* criteria for a mood disorder, which is consistent with previous studies (Averill et al., 2007), and approximately 9% met criteria for an adjustment disorder. Importantly, nearly all of the participants who met criteria for a current mood disorder reported being previously diagnosed with a mood disorder, suggesting that major depressive episodes in ALS represent the recurrence of an existing psychiatric disorder. Consistent with previous findings (Grossman et al., 2007), responses on the BDI-II indicated that depression symptom severity was relatively low in the sample, with a mean score well below the cut-off for clinical significance and approximately 81% of the sample reporting minimal or no depressive symptoms.

Based on review of the literature, this is the first study to report prevalence rates for DSM-IV-*TR* diagnoses of Adjustment Disorder with Depressed Mood *and* Adjustment Disorder with Mixed Anxiety and Depressed Mood. The prevalence of adjustment disorders in our sample may reflect the fact that data was collected during the patients' first evaluation at The Houston Methodist Hospital MDA-ALS Clinic, where ALS diagnoses were given for the first time or confirmed by multidisciplinary evaluation. Taken all together, our data demonstrated that depressive symptoms in ALS primarily manifest in one of two ways: either as a major depressive episode in the context of recurrent MDD or as an adjustment disorder in reaction to the diagnosis. Interestingly, endorsement of current mood disorders and patients' self-report of previous depression diagnoses (totaling 36.6% of the sample) is more than twice that of lifetime prevalence estimates of MDD in U.S. adults (16.5%; Kessler, Berglund, Demler, Jin, & Walters, 2005). As this study is the first to report current and previous mood disorder prevalence rates, it is unknown whether this finding is unique to our sample or generally reflective of patients with ALS. Lastly, approximately 25% of patients in this sample were experiencing clinically significant EL, well-within the ranges previously reported (Palmieri et al., 2009; Richter, 2005).

This is the first study to report prevalence rates and comorbidity of apathy, mood disorders, adjustment disorders, and EL simultaneously in a sample of patients with probable or definite ALS. Approximately 22% of patients were experiencing two or more of these neuropsychiatric disorders (Table 9). Notably, twice as many patients were experiencing comorbid apathy and EL (12%), compared to comorbid apathy and depression or comorbid depression and EL (each with 6%). Only 4 of 117 patients experienced all three disorders simultaneously. While these results speak to substantial comorbidity of these disorders in

ALS, these findings also supported the idea that these emotional states are dissociable, despite overlapping symptomatology. This theory was supported further by correlational analyses between these variables. Apathy showed a small, but significant, association with diagnosis of an adjustment disorder, but was not significantly related to either diagnosis of a mood disorder or EL. Diagnosis of a mood disorder was significantly, but weakly correlated with EL. Ultimately, these results show that apathy, depression, and emotional lability may co-occur, but are distinct in ALS as they are in other neurological disorders (Grossman et al., 2007; Havins, Massman, & Doody, 2013; Kirsch-Darrow, Marsiske, Okun, Bauer, & Bowers, 2011; Litvan, Mega, Cummings, & Fairbanks, 1996; Naarding, Janzing, Eling, van der Werf, & Kremer, 2009; Pluck & Brown, 2002; Tagariello, Girardi, & Amore, 2009; Witgert et al., 2010; Zahodne & Tremont, 2012).

Although very little literature on this topic exists, imaging studies in patients with ALS and other neurological and psychiatric disorders may explain why these neuropsychiatric symptoms frequently co-occur. Generally speaking, apathy, depression, and EL have all been linked to areas of the prefrontal cortex. In particular, the anterior cingulate cortex has been associated with apathy (Lavretsky et al., 2007; Woolley et al., 2011), depression (Bush, Luu, & Posner, 2000; Drevets, Savitz, & Trimble, 2008; Kostić & Filippi, 2011), and EL (Parvizi et al., 2001). Likewise, the orbitofrontal cortex has been associated with apathy (Levy & Dubois, 2006; Thobois et al., 2010), depression (Drevets, Savitz, & Trimble, 2008; Kostić & Filippi, 2011), and EL (Parvizi et al., 2001). In addition to these common areas that may explain comorbidity of these disorders, other studies have identified abnormalities in neuroanatomical areas that help distinguish the neuropathology of apathy, depression, and EL. For example, apathy has been consistently associated with basal ganglia

circuits (Levy & Dubois, 2006), and with abnormalities in the left frontal white matter and bilateral motor regions in patients with ALS (Woolley et al., 2011). As noted above, EL is associated with disruptions in corticobulbar (McCullagh et al., 1999) and corticocerebellar pathways (Parvizi et al., 2001). Lastly, depression has been associated with multiple areas of the frontal and medial temporal lobes, and in particular, damage to areas that connect the prefrontal cortex to areas of the limbic system (Arnold et al., 2012; Benoit & Robert, 2011; Lavretsky et al., 2007). Unfortunately, our understanding of distinct anatomical profiles associated with apathy, depression, and EL in ALS is limited by the fact that no study to date has studied all three disorders simultaneously in any patient population.

This study found surprisingly high rates of impaired verbal learning and memory in our sample of patients with ALS, particularly when compared with much lower rates of impaired phonemic fluency. The rate of FAS impairment in a subsample of patients who were administered both HVLT-R and FAS (9.5%) was similar to the percent of patients with impaired FAS in the full sample included in regression results (12.5%). However, the rates of FAS impairment in patients administered only FAS was nearly twice that in patients administered both measures (18.4% and 9.5%, respectively). The differences between these two subsets of patients could not be explained by differences in demographic or clinical variables. Similar differences in rates of impairment for verbal memory and phonemic fluency were found by Jelsone Swain et al. (2012) in a sample of 22 patients with ALS. In their study, 31.8%, 27.3%, and 4.5% of patients had scores more than 1.6 standard deviations below the mean on HVLT-R Immediate, HVLT-R Delayed, and the Controlled Oral Word Association Test (Benton, 1983), respectively. However, Massman et al. (1999) found nearly identical rates of impairment (by the same definition used in this study) for the California

Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987) learning trials 1-5 (20.0%) and FAS (21.2%) in a sample of 146 patients with ALS. Rates of verbal learning and memory deficits may vary across studies due to differences in sample sizes, measures used, and normative standards employed.

Hypothesis 2 was only partially supported by the results. Both continuous and dichotomous measures of apathy were significantly associated with measures of phonemic fluency and cognitive flexibility. This finding is partially consistent with Witgert et al. (2010), who also found an association between apathy and measures of mental flexibility and semantic fluency, but did not find an association with phonemic fluency. Clinically significant apathy accounted for nearly 6% of variance in TMTB scores, over and above upper extremity muscle function, clinically significant depression, and EL. Interestingly, when continuous apathy scores were entered into the model, apathy was no longer a statistically significant predictor of TMTB scores. Although apathy did not emerge as an independent predictor in the original analyses, continuous apathy scores did significantly predict numbers of perseverative responses committed on the WCST and accounted for nearly 8% of variance in scores, over and above the contributions of mood and adjustment disorder diagnosis, EL, and upper extremity muscle function. Apathy did not significantly predict performance on measures of auditory attention span, visuomotor processing speed, verbal memory, or verbal fluency. Our findings were different from those published by Grossman et al. (2007), who found that apathy predicted performance on measures of verbal fluency. As only the second known study examining a predictive relationship between apathy and cognitive functioning in ALS, our results suggest that apathy only minimally predicts performance on some measures of executive functioning. Given the overlap in frontal brain

areas thought to be responsible for apathy and mental flexibility, it may be that extramotor neurodegeneration in ALS is responsible for the emergence of both apathy and these particular cognitive deficits (Woolley et al., 2011). It is also possible that effort, either in the context of apathy or independently, influenced patients' performances on cognitive measures and thus the relationship between apathy and cognitive functioning.

The results of statistical analyses were consistent with hypotheses 3 and 4. Diagnosis of a mood or adjustment disorder was significantly correlated with auditory attention span, auditory working memory, and phonemic fluency, while a diagnosis of a mood disorder (i.e., MDD or Dysthymic Disorder) was only correlated with phonemic fluency. Importantly, once disease severity, apathy, and EL were accounted for, mood and adjustment disorders did not predict performance on any neuropsychological measure. Though not a hypothesis, there was weak evidence of some association between depression symptom severity scores and cognition, as higher BDI-II scores predicted fewer WCST perseverative responses committed, but did not predict performance on any other neuropsychological measure. To date, Jelsone-Swain et al. (2012) are the only other authors to examine the relationship between depression and cognition in ALS, and they did not report any significant relationship with individual cognitive measures. These investigators used two self-report depression inventories (GDS and BDI-II), rather than DSM-IV-*TR* diagnoses.

EL was significantly correlated with phonemic fluency and visuomotor processing speed. Although EL approached significance in predicting TMTA scores, it did not independently predict performance on any neuropsychological measure administered, after controlling for disease severity, apathy, and MAD. Our findings are partially consistent with the only other two studies to examine this relationship, as Palmieri et al. (2009) did not find

any significant associations between EL and cognitive measures and McCullagh et al. (1999) found a relationship only with WCST Categories. The differences in our findings may be explained by our considerably larger sample size, the fact that ours was a diagnostically homogenous group, and differences in neuropsychological measures used in the three studies.

Disease severity variables significantly correlated with nearly all of the neuropsychological variables (see Table 12). Furthermore, bulbar symptom severity independently predicted both semantic fluency and DSB scores. Upper extremity muscle function predicted both TMTA and TMTB. While this finding seems intuitive, given the manual output required by these tasks, the relationship between disease severity and cognitive impairment is debated in the existing literature (Gordon et al., 2010; Jelson-Swain et al., 2012; Massman et al., 1996). Conflicting findings may be explained by some investigators using total scores from disease severity measures (rather than subscores likely to affect performance on neuropsychological measures), as well as using a single composite score to represent cognitive functioning. If a significant relationship does exist, it is yet unclear whether disease severity predicts impaired neuropsychological test performance due to motor output demands or because overall neurodegeneration is causing both motor symptoms and cognitive impairment. Of course, several studies have shown that cognitive impairment exists even when controlling for disease severity and particular motor components of our tasks (Abrahams et al., 1997; Abrahams et al., 2000; Pettit 2013; Štukovnik, Zidar, Podnar, & Repovš, 2010). Together, previous reports and our results suggested that specific disease severity variables should be carefully considered when interpreting cognitive test results for patients with ALS.

This study has several potential limitations that warrant attention. First is the presence of missing neuropsychological test data as a result of patients' physical limitations and time constraints dictated by evaluations conducted in a clinical context. Second is the limited generalizability of our sample, given The Houston Methodist Hospital MDA-ALS clinic's status as a tertiary care center. Ultimately, the patients in our sample benefit from a level of care that may decrease their likelihood of developing neuropsychiatric disorders. In addition, the number of patients taking an antidepressant or Nuedexta could have limited the impact of these neuropsychiatric disorders on cognitive performance. On the other hand, if some patients taking these medications were still reporting clinically significant symptoms, it is likely that their neuropsychiatric symptoms were not well-managed. Also, the FrSBe was not designed to measure behavior change in a patient population with motor dysfunction. It is possible that some FrSBe apathy scores reflect behavioral dysfunction, as well as motor symptoms of ALS. In addition, the caregiver form was used, and the type and nature of the relationship of the informant was not included in the database. Informants who had less contact with patients may have provided less accurate information about the patients' behavioral changes. Finally, the number of regressions conducted might be cause for concern. However, we felt that the number and specific regressions conducted were necessary to provide a clear picture of the relationship between neuropsychiatric symptoms and cognitive performance in our sample.

While our study took steps to clarify the relationships of apathy, clinically significant depression, and EL to cognition in ALS, it is clear that more work in this area is needed. In the future, it will also be important to investigate the prevalence rates of apathy, depression, and EL longitudinally in patients with ALS. In addition, it will be helpful to determine

whether the presence of comorbid neuropsychiatric disorders (e.g., depression and apathy) is associated with disease severity or cognitive decline in patients with ALS. Given the prevalence rates reported here, it would also be helpful to investigate the neuroimaging correlates of apathy, depression, and EL in the same sample of patients with ALS, as well as any changes in prevalence of these disorders pre- and post-treatment for ALS. Lastly, in light of evidence of apathy predicting conversion to dementia in MCI and Parkinson's disease, future research should examine whether apathy predicts conversion from ALS to FTD.

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rized results of previous cognitive findings in ALS

orms	N (ALS, HC)	Summary of Results	Methodological Notes
HC	23 (14, 9)	Authors found significant differences between the groups on WCST, Paired Associate Test, and Williams delayed recall. No statistically significant differences were found on: WMS DS, Recall of Prose; ROCFT Copy or Immediate Recall.	
HC	31 (17, 14)	Patients with ALS performed significantly worse on measures of verbal fluency and nonverbal fluency. No differences were found between the groups on the WCST, Stroop Test, AVLT, or ROCFT.	Fluency tests do not appear to have validity and reliability data. Nonverbal fluency appears to be based on research with children.
%ile core	146	Percentages of patients performing below the 10th percentile on neuropsychological measures were as follows: 35.8% on the Short Category Test, 31.5% on VSAT Time, 28.1% on CRMT Accuracy, 35% on FAS, 29% on CVLT Total Learning, 15.8% on BNT, 13% on Line Orientation, and 12.5% on SDMT (best of Oral or Written Trial). Authors reported 35.6% of the sample scored below the 5th percentile on 2 or more measures.	
HC	80 (52, 28)	ALS participants' scores were significantly worse than healthy controls on the following measures: Written Verbal Fluency index, WCST Categories, WCST Total errors, Recognition Memory Test (Words). Authors found no differences between the groups on: NART, Paired Associate Learning, Recognition Memory Test (Faces), KOLT, WCST % perseverative errors, WCST trials to first category, Random Movement Joystick Test, Tower of Hanoi (computer version), and Stroop test.	
HC	42 (18, 24)	ALS participants' scores were significantly worse than healthy controls on the following measures: MMSE, Dementia Rating Scale, Letter fluency, Category fluency, Pyramids and Palm Trees test, Graded Naming Test, Test for the reception of grammar, WMS-R DS reverse. Authors found no differences between the groups on: National Adult Reading Test, WMS-R DS forwards, Picture Naming test, and Word-Picture matching test.	
HC	(13, NR)	ALS patient performed > 1 SD below the control group on only the Motor Free Visual Perception Test. No significant differences were found between the groups on WCST, Recognition Memory Test, RAVLT, Consonant Trigrams Test, Thurstone Written Word Fluency, or COWA.	

Abrahams et al. (2000)	HC	57 (22, 25)	ALS participants' scores were significantly worse than healthy controls on the following measures: Written Verbal Fluency Index, Written verbal fluency (raw), and Category fluency (raw). The authors found no significant differences between the groups on: Spoken Verbal fluency index, Category fluency index, Design fluency index, Spoken Verbal fluency (raw), Design fluency (raw)	Fluency measures were all adapted for use in ALS population. Authors do not reference validation studies.
Hanagasi et al. (2002)	HC	35 (22, 13)	ALS participants performed significantly worse than controls on the following measures: WAIS-R DS Backwards, CPT (Total Correct and commissions), DRT, SDLT, Stroop Test (1 and 5), Go-no-go Test (R hand commission), TMT (A, B, and B-A), FAS, Category fluency (Animals), BNT (Short form), CVLT (Total learning, 1st trial, SD Cued Recall, LD Free and Cued Recall, Perseverations), Benton Line Orientation, and WAIS-R BD. No significant differences were found between the groups on WAIS-R DS Forward, CPT Response Latency, Go-no-go (L commissions, response latency), CVLT (5th trial, SD Free Recall, Intrusions, or Recognition), or Benton Facial Recognition.	All spinal onset, depression excluded
Abrahams et al., 2004	HC	46 (28, 18)	ALS patients performed significantly worse on both written and spoken measures of verbal fluency, the Graded Naming Test, and a letter span test. No significant differences were found between the groups on category fluency, design fluency, WCST, PASAT, Paired Associate Learning, Recognition Memory Test, KOLT, Benton Line Orientation Test, or a Sentence Completion Test.	
Abrahams, Leigh, & Goldstein (2005)	HC	38 (20, 18)	ALS patients performed significantly worse than controls on both written and spoken measures of verbal fluency. No differences were found on other measures of executive functioning, memory, language, or visuospatial functions.	This study employed a longitudinal design. Only results from time 1 are reported here.
Ringholz et al. (2005)	HC	408 (279, 129)	Data from ALS patients and healthy controls were entered into cluster analysis, yielding 4 clusters: intact, mild impairment, moderate impairment, and severe impairment. Of the control participants, 95% fell in the intact cluster, compared to 49% of ALS participants. The remaining ALS patients were classified as mildly (32%), moderately (13%) or severely impaired (6%). All ALS groups (including those who were intact), performed significantly worse on WMS-R LM I and II, VR I and II, VSAT, and AMNART. Significant differences were also found between controls and each of the impaired ALS groups on the MMSE. No differences between the healthy controls and any ALS group was observed on the Benton Facial Recognition Test.	
Robinson et al. (2006)	HC	27 (19, 8)	Results of MANOVAs showed no significant differences between the groups on any measure at baseline or 6-month follow-up. At 6 months,	Exclusionary criteria: any behaviors or clinical findings indicative of

			6 ALS patients performed ≥ 1 SD below the mean on at least one neuropsychological test. Impaired performance was demonstrated by 3 patients on RAVLT Trial 1, 3 on WCST (# Categories), and 1 patient each on RAVLT Trial 5, RAVLT Recognition Memory, WMS-R Recognition DS Reverse, Raven's Colored Progressive Matrices (% correct) and Object Decision Task (% correct). No patients had impaired performance on WMS-R Recognition DS Forward, Peabody Verbal Learning Test, or Efron Shapes Discrimination Test.	cognitive deficits and depression, as observed by the multidisciplinary team.
Röttig et al. (2006)	HC	44 (29, 15)	Authors found significant differences between the groups on one measure of verbal fluency (alternating; between male Christian names and colors). No differences were found on the remaining cognitive measures: Verbal Fluency (phonemic, letters LBS; semantic, supermarket items), Conditional Associative Learning Task (verbal and nonverbal), SDMT, or CVLT.	Only alternating fluency held up after applying more stringent criteria for multiple analyses; overall, verbal fluency tasks did not have citations; Included only limb-onset patients
Mezzapesa et al. (2007)	HC	18 (9, 9)	ALS patients' scores were significantly lower than controls' only on SDMT. Authors found no statistically significant differences on the MMSE, Brown-Peterson Interference Test, FAS, or Stroop Color/Word Interference Test.	Patients with DSM-IV diagnosis of dementia, behavioral changes indicative of FTD, or several bulbar signs were excluded.
Pinkhardt et al. (2008)	HC	40 (20, 20)	Statistically significant differences were found between the groups on COWA (FAS), 5-point Fluency Test, and TAP attention incompatibility subtest. No differences were found on Stroop's Colour Word Interference Test or COWA (Animals).	Verbal fluency was modified to allow patients to either speak or write the words generated.
Evdokimidis et al. (2002)	HC	79 (51, 28)	ALS patient's scores were significantly worse on WCST. Authors found no statistically significant differences between the groups' VIQ, Stroop, or ROCFT Delayed Memory scores.	Controls were patient's subjects. Patient with VIQ < 70 and BDI > 16 were excluded.
Girardi, MacPherson, & Abrahams (2011)	HC	39 (19, 20)	There were no significant differences between groups on the NART-R FSIQ, Graded Naming Test, or Verbal Fluency index. ALS patients showed learning deficits on a modified and shortened version of the Iowa Gambling Task.	Two separate studies reported in the same paper. No overlap in participants between the two.
	HC	34 (14, 20)	ALS participants' scores were significantly worse than healthy controls on WMS-III LM I, the Judgment of Preference task, Facial Expressions of Emotion Test, and trended towards significance for Reading the Mind in the Eye. No significant differences were found on the following measures: WASI VIQ, WMS-III Percent Delayed Recall, KOLT total, Graded Naming Test, Hayling Sentence Completion Test (errors, and response time), Brixton Spatial Anticipation Test (errors), or Verbal Fluency index.	
Phukan et al. (2012)	HC	242 (132, 110)	Authors found significant differences between the groups on the following measures: phonemic verbal fluency, category fluency	Final sample included 160 participants with ALS; however,

			(Animals), Stroop Colour-Word Test. No statistically significant differences were found on WMS-III Backwards DS or Brixton Spatial Anticipation Test. Authors also compared the number of participants in each group who had impaired (≥ 2 SD below the mean) performance on the above measures. Significantly more ALS patients showed impairment on both measures of fluency, Stroop Colour-Word Test, and Backwards DS.	only 132 patients without dementia were included in the comparison analyses. Not all participants had data for all tests.

BD = Block Design; BDI = Beck Depression Inventory; BNT = Boston Naming Test COWA = Controlled Oral Word Association; CPT = Continuous Performance Test; CVLT = California Verbal Learning Test; CRMT = Continuous Recognition Memory Test; DRT = Delayed recognition test; DS = Digit Span, FTD = Frontotemporal Dementia; FSIQ = Full Scale IQ; KOLT = Kendrick Object Learning Test; LM = Logical Memory; MMSE = Mini Mental State Examination; NART = National Adult Reading Test; NR = not reported; PASAT = Paced Auditory Serial Addition Test; RAVLT = Rey Auditory Verbal Learning Test; ROCFT = Rey Osterrieth Complex Figure Test; SDLT = Serial digit learning test; SDMT = Symbol Digit Modalities Test; VR = Visual Reproduction; VSAT = Verbal Series Attention Test; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale

Appendix 2. Summary of Hierarchical Regression Analyses for Dichotomous Predictors

	Step 1			Step 2		
Variable	B	SE	β	B	SE	β
DSF						
AALS Bulbar Score	-.02	.02	-.14	-.02	.02	-.11
Apathy				-.16	.17	-.09
MAD				-.31	.21	-.15
EL				-.09	.20	-.05
R^2			.02			.06
F			2.09			1.73
ΔR^2			.02			.04
ΔF			2.09			1.6
DSB						
AALS Bulbar Score	-.04	.02	-.23*	-.04	.02	-.24*
Apathy				-.06	.18	-.04
MAD				-.33	.22	-.15
EL				.10	.21	.05
R^2			.05		.08	
F			5.71*		2.1	
ΔR^2			.05		.03	
ΔF			5.71*		.91	
HVLT-R Immediate						
AALS Bulbar Score	-.06	.03	-.24	-.07	.04	-.25
Apathy				.03	.37	.01
MAD				.21	.42	.06
EL				.09	.40	.03
R^2			.06			.06
F			3.68			.98
ΔR^2			.06			.01
ΔF			3.68			.13
HVLT-R Delayed						
AALS Bulbar Score	-.07	.04	-.23	-.07	.04	-.24
Apathy				.16	.39	.06
MAD				.23	.45	.07
EL				.10	.42	.03
R^2			.05			.07
F			3.42			1.00
ΔR^2			.05			.01
ΔF			3.42			.25
Animals						
AALS Bulbar Score	-.05	.02	-.27**	-.05	.02	-.25*
Apathy				-.12	.25	-.05
MAD				-.22	.30	-.08
EL				-.02	.29	-.01
R^2			.07			.08
F			8.31**			2.31
ΔR^2			.07			.01
ΔF			8.31**			.36

	Step 1			Step 2		
Variable	B	SE	β	B	SE	β

FAS						
AALS Bulbar Score	-.03	.02	-.16	-.01	.02	-.06
Apathy				-.32	.19	-.16
MAD				-.25	.23	-.10
EL				-.35	.22	-.16
R^2			.03			.11
F			2.81			3.16*
ΔR^2			.03			.08
ΔF			2.81			3.21*
TMTA						
AALS UE Function	-.09	.02	-.39**	-.08	.02	-.35**
Apathy				-.11	.27	-.04
MAD				.23	.31	.07
EL				-.51	.27	-.19
R^2			.15			.19
F			16.49**			5.18**
ΔR^2			.15			.04
ΔF			16.49**			1.34
TMTB						
AALS UE Function	-.14	.03	-.41**	-.12	.03	-.40**
Apathy				-1.01	.39	-.26**
MAD				.27	.45	.06
EL				.11	.39	.03
R^2			.17			.23
F			19.02**			6.68**
ΔR^2			.17			.06
ΔF			19.02**			2.30
WCST Persev.Errors						
AALS UE Function	.26	.16	.20	.25	.17	.19
Apathy				2.24	2.50	.12
MAD				-2.68	2.93	-.12
EL				.15	2.31	.01
R^2			.04			.06
F			2.70			.97
ΔR^2			.04			.02
ΔF			2.70			.42

AALS UE Function = Appel ALS Scale Upper Extremity Motor Function; MAD = DSM-IV-*TR* mood or adjustment disorder; EL = emotional lability; DSF = Digit Span Forward; DSB = Digit Span Backward; HVLT-R = Hopkins Verbal Learning Test-Revised; TMTA = Trail Making Test part A; TMTB = Trail Making Test part B; WCST = Wisconsin Card Sorting Test