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Self-Regulation and Executive Functioning as Related to Survival in Motor Neuron Disease: Preliminary Findings

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Abstract

Objective—Disease progression varies widely among patients with motor neuron disease (MND). Patients with MND and coexisting dementia have shorter survival. However, implications of mild cognitive and behavioral difficulties are unclear. The present study examined the relative contribution of executive functioning and self-regulation difficulties on survival over a 6-year period among patients with MND, who scored largely within normal limits on cognitive and behavioral indices.

Methods—Patients with MND (N=37, age=59.97±11.57, 46% female) completed the Wisconsin Card Sorting Task (WCST) as an executive functioning perseveration index. The Behavior Rating Inventory of Executive Functions (BRIEF-A) was used as a behavioral measure of self-regulation in two subdomains self-regulatory behavior (Behavioral Regulation) and self-regulatory problem-solving (Metacognition). Cox proportional hazard regression analyses were used.

Results—In total, 23 patients died during follow-up. In Cox proportional hazard regressions adjusted for a priori covariates, each 10-point T-score increment in patient-reported BRIEF-A self-regulatory behavior and problem-solving difficulties increased mortality risk by 94% and 103%, respectively (adjusted HR=1.94, 95% CI [1.07, 3.52]; adjusted HR=2.03, 95% CI [1.19, 3.48]). In sensitivity analyses, patient-reported self-regulatory problem-solving remained significant independent of disease severity and a priori covariates (adjusted HR=1.68, 95% CI [1.01, 2.78]), though the predictive value of self-regulatory behavior was attenuated in adjusted models

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Conflicts of Interest

The authors declare no conflicts of interest.

(HR=1.67, 95% CI [0.85, 3.27]). Caregiver-reported BRIEF-A ratings of patients and WCST perseverative errors did not significantly predict survival.

Conclusions—Preliminary evidence suggests patient-reported self-regulatory problem-solving difficulties indicate poorer prognosis in MND. Further research is needed to uncover mechanisms that negatively affect patient survival.

Keywords

motor neuron disease; amyotrophic lateral sclerosis; survival; executive function; self-regulation; behavior

Motor neuron disease (MND) is class of neurodegenerative diseases characterized by a combination of upper and/or lower motor neuron degeneration. Two MND subtypes affect upper motor neurons in the cortex: amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS). Progression rates vary widely among patients with MND. Accumulating evidence has revealed that cognitive and behavioral deficits frequently coexist with MND (1). These deficits may affect survival and prognosis for patients with MND. However, the relative contribution of cognitive and behavioral deficits to patient survival is unclear.

The cognitive and behavioral profile of MND comprises a range of difficulties ranging from mild to severe. Deficits typically resemble those in frontotemporal dementia (FTD), including executive dysfunction and socioemotional behavior changes (2). Executive functioning is a cognitive domain comprised of high-order mental abilities that support goal-oriented tasks and novel problem-solving such as cognitive flexibility, inhibition, working memory, cognitive monitoring, and planning. The integrity of self-regulation may also be relevant to patients with MND. Self-regulation is goal-oriented, self-monitoring behavior, which comprises socially appropriate behavior, emotion regulation, thought regulation, and persistence. Self-regulation is thought to require executive functioning abilities (3). Though previous MND research has focused on deficits in patients with ALS, similar cognitive and behavioral impairments have also been observed in patients with PLS (4,5,6).

Coexisting dementia affects survival in MND. Patients with ALS and FTD have shorter survival than patients with either diagnosis alone (7,8,9,10). Among patients with both ALS and dementia, only those with caregiver-reported behavioral deficits had shorter survival (11). Subclinical cognitive and behavioral difficulties may also be relevant for disease prognosis. Worse executive functioning (indexed by diverse neuropsychological tests; 7,9) and behavioral impairments (indexed by the Cambridge Behavioural Inventory-Revised Apathy subscale and the Amyotrophic Lateral Sclerosis-Frontotemporal Dementia Questionnaire [ALS-FTD-Q]; 12,13) predicted shorter survival in patients with ALS without dementia. Additionally, a multi-domain cognitive composite predicted shorter survival, with executive, memory, and language tests making the greatest predictive contributions (14). Moreover, both patients with subclinical executive dysfunction and patients with ALS-FTD may experience faster motor symptom progression, suggestive of more aggressive disease. In a longitudinal study, ALS-FTD significantly predicted faster bulbar dysfunction progression. Similarly, patients with ALS-FTD and patients with executive dysfunction but without FTD exhibited a trend towards higher rates of overall functional decline (15).

Yet, the survival implications of cognitive and behavioral difficulties in patients with MND are unclear. In one study, the presence of cognitive impairment, defined as scoring 1.5 standard deviations below a normative group in any two cognitive domains, was not correlated with survival time (16). Another reported that a multi-domain cognitive composite did not predict survival in patients with ALS (17). Patients identified as having mild cognitive or behavioral impairments (using the ALS Brief Cognitive Assessment and the Frontal Systems Behavior Scale family form) did not have shorter survival than those classified as normal (11,9). Moreover, cognitive and behavioral measures appear to be differentially sensitive to mortality risk in MND. Among patients with ALS, dichotomized impairments on a broad cognitive screen (Addenbrooke's Cognitive Examination-Revised) and a behavioral measure (ALS-FTD-Q) were associated with significantly shorter survival. However, impairments on another executive functioning cognitive screen (Frontal Assessment Battery) and behavioral screen (Motor Neurone Disease Behavioural Scale) did not predict survival (13).

The present study examined two self-regulation ratings (patient- and caregiver-reported) and executive functioning test performance as continuous predictors of survival in a broad MND sample. The relative contributions of these cognitive and behavioral difficulties on survival were examined over a 6-year period. Our hypothesis was that worse self-regulation and executive functioning would predict shorter survival in patients with MND.

Method

Participants and Procedure

Participants with MND were recruited for a study examining self-regulation and cognitive functioning. Patients were recruited from ALS clinics at the Kentucky Neuroscience Institute at the University of Kentucky and Cardinal Hill Rehabilitation Hospital in Lexington, Kentucky. Data collection began in February 2009; survival data were gathered through June 2015. Patients completed the Wisconsin Card Sorting Test (WCST; 18) via computer and questionnaires were administered verbally to patients. Caregivers rated patients' self-regulation abilities independently in a separate room. Most patients were tested at the research site ($n = 30$); patients unable to travel were tested in their home ($n = 7$). The University of Kentucky Institutional Review Board approved the study and informed consent was obtained from all participants. Additional psychological measures were collected as part of the original study protocol. Participants were compensated \$50 for their participation.

Participants were 37 patients with MND (31 ALS, 6 PLS; 20 men, 17 women) and 36 caregivers (10 men, 26 women). Demographic data are reported in Table 1. Average ALS Functional Rating Scale-Revised (ALSFRRS-R; 19) score was 30.03 ($SD = 8.83$; range = 13-46). Eight patients (21.62%) reported bulbar onset and 29 (78.38%) limb onset. Seven patients (18.91%) were using non-invasive ($n = 6$) or invasive ventilation ($n = 1$) at the time of assessment. Patients were not screened for the presence of dementia. Therefore, patients represent a broad community sample of patients with MND. Eligibility criteria included: patient diagnosis of probable or definite ALS or PLS (20,21); diagnosis more than six months prior to enrollment, age 30-90 years; no patient diagnosis of Type 1 Diabetes; fluency in English; patient ability to provide informed consent (i.e., not have a legally

authorized representative); and a caregiver willing to participate. This sample provided adequate power (.90) to detect a large effect ($r = .50$) of executive functioning and self-regulation.

Measures

Demographics and disease characteristics—Participants reported their age, education, sex, symptom onset date (for disease duration calculation; years since onset at assessment date), onset site (bulbar or limb), diagnosis type (ALS or PLS), and diagnosis date.

Disease severity—Disease severity was assessed with the ALSFRS-R (19), a 12-item measure that assesses patients' functional abilities including: speech, salivation, swallowing, handwriting, utensil use, dressing and hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and need for ventilator support. Each functional ability is rated on a 0 to 4 scale; lower scores indicate greater disease severity (i.e., worse functional ability). Total scores range from 0 (worst functional ability) to 48 (intact functional ability). The ALSFRS-R demonstrated adequate internal consistency ($\alpha = .83$). The ALSFRS-R was administered by a single rater (principal investigator; ARR), who was trained by the neurologist leading the Multidisciplinary ALS Clinic Certified Treatment Center of Excellence (third author; EJK). Patients and their caregivers were interviewed together and consensus ratings were used to assess functional abilities. A dichotomous variable (yes/no) combined invasive and non-invasive ventilation use from ALSFRS-R item 12 for use as an a priori covariate. The ALSFRS-R total score was also used as a covariate for sensitivity analyses.

Executive functioning—Patients' executive functioning was assessed with the WCST, an index of perseveration and abstract thinking (18). The task involves utilizing feedback to sort 128 cards by color, shape, or number in response to shifts in sorting rules. The WCST provides various performance indices; the present study utilized age- and education-normed perseverative errors, reflecting cognitive inflexibility.

Self-regulation—Patients' self-regulation was assessed with the Behavior Rating Inventory of Executive Functions adult version (BRIEF-A; 22) via patient and caregiver reports of patients. The BRIEF-A is a 75-item behavioral index of self-regulation in patients' everyday environment, producing two subdomain scores reflective of self-regulation as it pertains to behaviors and emotions (i.e., 'Behavioral Regulation' subdomain) and self-regulation as it pertains to problem-solving and goals (i.e., 'Metacognition' subdomain). Both subdomains demonstrated adequate internal consistency for patient (Behavioral Regulation $\alpha = .85$; Metacognition $\alpha = .93$) and caregiver reports (Behavioral Regulation $\alpha = .91$; Metacognition $\alpha = .94$). The behaviors and emotions subdomain (Behavioral Regulation) assesses everyday problems in inhibition, shifting, emotional control, and self-monitoring (e.g., "I say things without thinking", "I am impulsive", and "I get upset quickly or easily over little things"). The problem-solving and goals subdomain (Metacognition) assesses everyday problems in initiation, working memory, planning/organization, task monitoring, and organization of materials (e.g., "I forget instructions easily", "I lose things (such as keys, money, wallet, etc)", and "I make careless errors when completing tasks"; 22).

Notably, the term ‘metacognition’ may be used to refer to various aspects of introspection, including either one’s *appraisal* of one’s own thoughts, cognitive functioning, and self-regulation (in this case, around goals and problem-solving) *or* one’s *ability to monitor and appraise* one’s own thoughts, cognitive functioning, and self-regulation (i.e., introspection accuracy and insight). In the present study, patient-reported BRIEF-A Metacognition subdomain scores refer to the former. For clarity, we refer to the abilities indexed by the BRIEF-A Metacognition subdomain as ‘self-regulatory problem-solving’ and capitalize ‘Metacognition’ when referring to the BRIEF-A subdomain name. The present study utilized both subdomains; scores are standardized by patient age. Higher T-scores reflect more self-regulation difficulty; T-scores ≥ 65 are considered clinically significant (22). Sensitivity analyses were conducted after removing items potentially related to the physiological process of MND (e.g., “taps fingers or bounces legs”, “has trouble sitting still”, “lies around the house a lot”) to assess for bias due to motor impairment. The following items were removed from the BRIEF-A for sensitivity analyses, Inhibit subscale items: 5 and 16; Initiate subscale items: 14 and 20; and Organization of Materials subscale items: 7, 40, 60, and 74.

Psychological distress—Patients’ psychological distress was assessed with the McGill Quality of Life Questionnaire (MQOL; 23). The MQOL assesses four domains: Physical Symptoms, Psychological Symptoms, Outlook on Life, and Meaningful Existence. The MQOL demonstrated adequate internal consistency ($\alpha = .90$). The present study utilized the Psychological Symptoms subscale to assess whether psychological distress accounted for relationships between patient-reported self-regulation difficulties and survival. The Psychological Symptoms subscale includes three items that assess patient-reported feelings of depression, worry, and sadness over the past two months. One missing value for one patient was replaced with the sample mean.

Survival—An approximately 6-year follow up was conducted in June 2015 in order to collect survival data. Dates of death were obtained via medical records and public obituary data. Survival time was defined as time from assessment date to death or censoring.

Data Analysis

Cox proportional hazard regressions were conducted in SAS (version 9.4) PROC PHREG to predict survival adjusting for covariates. A priori covariates included age, disease type (ALS or PLS), onset site (bulbar or limb), disease duration (symptom onset to assessment date), and dichotomous ventilation use (invasive and non-invasive), which are known to impact survival in patients with MND (21,24,25). One patient was on continuous invasive ventilation at enrollment, excluding this patient had no substantive effect on the results, and so results including all patients are reported. Executive functioning (WCST) and self-regulation (BRIEF-A) were used as continuous predictors of patient survival; values were sample mean centered and scaled so that hazard ratios (HR) were expressed per 10 T-score points. All predictors and covariates were normally distributed; though WCST perseverative errors were slightly skewed (skewness = 1.04, $SE = .39$), no significant outliers were present, and thus these data were not transformed. Survival analyses were performed on time from assessment date to death or censoring. Significant predictors were further assessed for

the proportional hazards assumption using the supremum test with 10,000 replications; in all cases, the assumption was met.

Results

Regarding self-regulation, 16.22% of patients rated their own self-regulatory behavior and 18.92% of patients rated their own self-regulatory problem-solving abilities (i.e., BRIEF-A Behavioral Regulation and Metacognition subdomains respectively) within the clinically impaired range ($T = 65$), compared with self-ratings by others similar in age from which normative data are derived (see Table 2). Based on caregivers' reports, 5.56% of patients' self-regulatory behavior and 13.89% of patients' self-regulatory problem-solving abilities were rated within the impaired range. Patient and caregiver reports of patient self-regulation were positively correlated with medium effect sizes, but not statistically significant (Behavioral Regulation subdomain, $r = .28$, $p = .10$; Metacognition subdomain, $r = .33$, $p = .052$). Patients rated their self-regulation abilities as significantly more impaired (BRIEF-A Total T-score $M = 57.61$, $SD = 10.12$) than did their caregivers ($M = 50.81$, $SD = 8.28$; $t(35) = 3.68$, $p = .001$). Regarding executive functioning, 16.22% of patients' WCST perseverative errors performance fell within the impaired range ($< 16^{\text{th}}$ percentile) compared to others with similar age and education, though none performed $< 5^{\text{th}}$ percentile. Median disease length calculated from diagnosis to death or censoring was 4.27 years ($SD = 4.50$; median from symptom onset = 5.48 years, $SD = 5.06$; see Table 1). At censoring, 23 patients had died (62.2%; ALS $n = 22$; PLS $n = 1$) and 14 were alive (37.8%; ALS $n = 9$; PLS $n = 5$).

In the Cox proportional hazard regressions testing the primary hypotheses, patient survival was significantly predicted by patient-reported self-regulation adjusted for a priori covariates (age, disease type, onset site, disease duration, and ventilation use). For each 10-point T-score increment in self-regulatory behavior difficulties (Behavioral Regulation subdomain), mortality risk increased by 94% (adjusted HR = 1.94, 95% CI [1.07, 3.52], $p = .029$). For each 10-point T-score increment in self-regulatory problem-solving difficulties (Metacognition subdomain), mortality risk increased by 103% (adjusted HR = 2.03, 95% CI [1.19, 3.48], $p = .009$). In contrast, caregiver-reports of patient self-regulation did not significantly predict patient survival (Behavioral Regulation subdomain adjusted HR = 0.96, 95% CI [0.48, 1.94], $p = .92$; Metacognition subdomain adjusted HR = 1.11, 95% CI [0.70, 1.78], $p = .66$), nor did WSCT perseverative errors (adjusted HR = 1.40, 95% CI [0.81, 2.40], $p = .22$). Figures 1 and 2 show survival predicted by patient-reported self-regulatory behavior and self-regulatory problem-solving respectively. Although continuous variables were assessed in the statistical models, self-regulation is trichotomized for illustrative purposes. Survival curves show the model-predicted survival and survival curve for patient-reported self-regulation scores at 10 T-score points below the sample mean (L = low), at the sample mean (M = mean), and 10 T-score points above the sample mean (H = high), where higher T-scores indicate more self-regulation difficulty.

Although we ran five tests of a priori hypotheses (i.e., patient and caregiver-reported BRIEF-A Behavioral Regulation and Metacognition subdomains and WCST), conservatively, a Bonferroni-adjusted p value could be applied to the five outcomes (adjusted $p < .01$). The a priori patient-reported self-regulatory problem-solving model would remain statistically

significant (a priori model $p = .009$), though the self-regulatory behavior model would not (a priori model $p = .029$). Next, post hoc sensitivity analyses assessed the impact of potential confounds. First, sensitivity analyses were conducted after removing BRIEF-A items potentially biased by motor impairment and the physiological process of MND (see Table 3). Raw score predictors were scaled so that HRs were associated with 10-point increments (equal to approximately 1 SD for both subdomains). Results for patient-reported self-regulatory behavior (Behavioral Regulation subdomain; adjusted HR = 2.74, 95% CI [1.28, 5.83], $p = .009$) and self-regulatory problem-solving (Metacognition subdomain; adjusted HR = 2.47, 95% CI [1.31, 4.64], $p = .005$) remained statistically significant. These sensitivity analyses utilized raw scores and therefore BRIEF-A scores were not standardized by age, though age was included as a covariate in these models. Second, sensitivity analyses added total ALSFRS-R as a covariate. One patient was excluded from this analysis; due to time constraints, the rater did not complete the ALSFRS-R for this patient. For each 10-point T-score increment in the patient-reported self-regulatory problem-solving difficulties, mortality risk increased by 68% (adjusted HR = 1.68, 95% CI [1.01, 2.78], $p = .044$), though patient-reported self-regulatory behavior was no longer statistically significant (adjusted HR = 1.67, 95% CI [0.85, 3.27], $p = .14$). As before, caregiver-reported BRIEF-A scores (Behavioral Regulation subdomain adjusted HR = 0.77, 95% CI [0.36, 1.67], $p = .52$; Metacognition subdomain adjusted HR = 1.01, 95% CI [0.60, 1.72], $p = .96$) and WCST (adjusted HR = 1.15, 95% CI [0.65, 2.04], $p = .63$) were not statistically significant. Third, although MND type (ALS or PLS) was included as an a priori covariate, sensitivity analyses were conducted on the ALS subsample ($n = 31$). For each 10-point T-score increment in patient-reported self-regulatory problem-solving difficulties, mortality risk increased by 102% (adjusted HR = 2.02, 95% CI [1.17, 3.52], $p = .01$), though the effect of patient-reported self-regulatory behavior decreased in size and was no longer statistically significant (adjusted HR = 1.65, 95% CI [0.90, 3.01], $p = .10$). As before, caregiver-reported BRIEF-A scores (Behavioral Regulation subdomain adjusted HR = 0.83, 95% CI [0.40, 1.74], $p = .62$; Metacognition subdomain adjusted HR = 1.05, 95% CI [0.64, 1.72], $p = .84$) and WCST (adjusted HR = 1.74, 95% CI [0.95, 3.17], $p = .07$) were not statistically significant. These sensitivity analyses support the primary results and suggest that the association between patient-reported self-regulatory problem-solving and survival is substantive and not an artifact of motor impairment bias or disease severity. However, the observed statistical effects of self-regulatory behavior may overlap with those of motor impairment.

Because patient-reported but not caregiver-reported self-regulation difficulties predicted survival and patients rated themselves as significantly worse than their caregivers, potential factors affecting discrepancy between patients and their caregivers were examined. One possibility is that patients are more aware than caregivers of executive function difficulties as they manifest in self-regulation. However, correlations between patient executive functioning performance (WCST) and patient- and caregiver-reported self-regulation (BRIEF-A) were small and not statistically significant ($r_s = -.17 - .01$, $p_s = .33 - .95$). However, the present study did not include ratings of patients' perception of their own performance on the WCST, which may be used to assess cognitive insight (26). Additionally, executive abilities assessed via WCST perseverative errors do not necessarily correspond to the everyday self-regulation abilities patients and their caregivers reported on

the BRIEF-A. Another possibility is that patients' self-regulation ratings were affected by generally negative self-appraisal and psychological distress, and this negativity accounted for the underlying association with survival. However, patient psychological distress, assessed by the MQOL Psychological Symptoms subscale, did not predict patient survival (adjusted HR = 0.97, 95% CI [0.90, 1.05], $p = .42$). Adding patient psychological distress as a covariate resulted in little change to results for patient-reported self-regulatory problem-solving (adjusted HR = 2.01, 95% CI [1.17, 3.46], $p = .012$) and self-regulatory behavior (adjusted HR = 1.95, 95% CI [1.08, 3.53], $p = .028$).

Discussion

Severe behavioral deficits impact survival among patients with ALS and coexisting dementia (11). Recently, behavioral deficits were also found to predict shorter survival among patients with ALS without dementia (12,13). The present findings extend these observations and demonstrate that mild behavioral difficulties, as indicated by patient-reported self-regulation, also predict survival in patients with MND. Adjusting for patient age, disease type, onset site, disease duration, and ventilation use, mortality risk roughly doubled for each 10-point T-score increase in patient-reported self-regulation difficulties. Patient-reported self-regulation difficulties with everyday problem-solving and goals (e.g., poor initiation, working memory, task monitoring, planning/organization, and organization of materials as indexed by the BRIEF-A) were especially predictive of survival. Patients' self-regulation difficulties were not explained by generally negative self-appraisal and psychological distress, which was not itself associated with survival. In patients with ALS, behavioral deficits may be independent from mood (1). Additionally, patient-reported self-regulatory problem-solving remained a robust survival predictor after removing items potentially biased by motor impairment, after adjusting for disease severity (i.e., total ALSFRS-R), and within the ALS phenotype alone.

Poorer prognosis among patients with self-regulation difficulties could reflect a more aggressive form of MND. It is also plausible that self-regulation difficulties and other non-motor symptoms may be biomarkers of disease progression in MND. Presently, ALS/MND disease severity and progression are defined by motor symptoms captured via functional rating scales, which raises the question whether non-motor symptoms should be assessed similarly to rating scales for other neurodegenerative diseases. For example, the Unified Parkinson's Disease Rating Scale-Revised includes non-motor symptoms common in Parkinson's disease including cognitive impairment, psychosis, apathy, and depression (27).

Alternatively, patients with severe behavioral deficits have poorer compliance with recommendations for respiratory support and percutaneous endoscopic gastrostomy (24). Patients with self-regulation difficulties may also be less compliant with supportive care, affecting survival. Conversely, better self-regulation could also aid patients' ability to follow multidisciplinary care regimens. Patients with better self-regulation may have a slower manifestation of the disease, or good self-regulation could indicate more cognitive and physical reserve. Further research is needed to better understand the mechanism(s) by which behavioral deficits negatively impact patient prognosis.

In the present study, patients and their caregivers reported similar patterns of patients' self-regulation abilities, though patients' reports of their own self-regulation abilities were worse than the ratings their caregivers gave them. Moreover, caregiver reports of patients' self-regulation did not significantly predict patients' survival, though results were in the expected direction. Notably, the present results are drawn from a broad community sample of patients with MND, who as a sample scored largely within normal limits on executive functioning and self-regulation indices, though some patients exhibited clinical impairments. Caregiver assessment of patients' behavioral deficits is common practice for this patient population. Patients with severe behavioral deficits, such as those with FTD, may experience loss of insight (26). Yet, the impact of mild impairments on insight and self-awareness is unclear. For example, previous research has demonstrated that, in contrast to patients with Alzheimer's disease who lack insight, patients with mild cognitive impairment are able to identify everyday self-regulation and executive behavior difficulties in themselves (28). Less is known about insight in ALS/MND, though preliminary research suggests patients with ALS without FTD have normal insight, contrasting those with ALS-FTD who lack insight (29). In previous research, patients with ALS without FTD, who were rated as having "normal" behavior by their informant, self-reported more behavioral change, clinically significant apathy, and significantly higher disinhibition than their informants (29). The present results suggest that when it comes to mild behavioral and self-regulation problems, patients with MND have intact awareness of their difficulties and these patient-reported difficulties have prognostic value. It is plausible that certain behavioral aspects that assess internal processes may not be as apparent to an observer (2). Regarding the present study, the BRIEF-A is attuned to subtle self-regulation difficulties including several internal processes such as problem-solving abilities (e.g., on-line task monitoring, concentration, or working memory), inhibiting impulses, and emotional control, which in some instances may not be observable by an informant. Therefore, certain self-regulation aspects captured by the BRIEF-A that assess internal processes may not be as apparent to patients' caregivers as to patients themselves. In contrast, behavioral measures previously applied to ALS/MND (e.g., Frontal Systems Behavior Scale, Frontal Behavioral Inventory; 30,31) typically assess severe "frontally mediated" behavioral deficits common among patients with FTD, such as violation of social mores, which may be better rated by an informant. Nonetheless, the present study draws attention to gaps in the ALS/MND literature regarding insight, which warrant future research.

Finally, the present study also examined executive dysfunction, specifically cognitive inflexibility, and found that patients' WCST perseverative errors did not significantly predict survival, though results were again in the expected direction. Neuropsychological test performance has produced variable associations with survival in ALS/MND. Previous studies that examined executive functioning distinctly tended to find significant relationships with survival (7,9,14), whereas studies that examined multi-domain cognitive deficits or brief cognitive screens did not (11,16,17). However, executive functioning has several subcomponents, which correlate to one another to varying degrees (32), and relatedly, neuropsychological tests are differentially sensitive to mortality risk and prognosis in ALS/MND. Regarding the present results, it is possible that cognitive inflexibility, indexed by WCST perseveration, does not impact survival in MND, though other types of executive

dysfunction do impact survival (e.g., poor rule attainment, response generation, sustained attention, divided attention, working-memory, planning, abstract reasoning, or inhibition; 7,9,14). Another possibility is that the present study was underpowered to detect a significant relationship between executive functioning and survival. Though the present study does not provide conclusive results regarding executive functioning and survival in ALS/MND, results suggest that relationships between performance-based executive functioning measures and survival merits further research. Particularly, which subcomponent(s) of executive functioning potentially drive relationships with mortality risk.

The following limitations of the present study should be considered. First, small sample size may have limited our ability to detect a significant relationship between executive functioning and survival, especially if the effect was medium to small. Moreover, the present results warrant replication in a larger sample. Second, our executive functioning assessment is limited to WCST perseverative errors alone; additional research examining other executive subcomponents is needed. Third, previous research suggests that apathy is the most common behavioral impairment in patients with ALS (1). The behavioral measure utilized in the present study, BRIEF-A, is limited in that it does not assess apathy separately, though some items address apathy (e.g., “I have difficulty getting excited about things”; 22). Fourth, although patient-reported psychological distress did not account for the underlying relationship between patient-reported self-regulation and survival, this study is limited in that it did not include a caregiver-rated indicator of patients’ negative affect or psychological distress, which may have provided further information about discrepancies between patient and caregiver reports and test performance. Fifth, in many MND clinical trials mortality is recorded as either natural death or onset of continuous ventilation support. The present study utilized natural death, as date of ultimate use of continuous ventilation support was unknown. Using more stringent mortality endpoints can strengthen future research. Sixth, patients were not formally screened for the presence of dementia; patients represent a broad community sample of patients with MND. Finally, it is unclear whether self-regulation difficulties are attributable to the disease process or whether these were premorbid characteristics. However, the relationship with survival and possible prognostic value remain compelling regardless of etiology.

The present study also has several strengths. First, previous research suggests that the BRIEF-A is sensitive to subtle changes in cognition, emotion, and behavior regulation that performance-based executive functioning tasks may not capture and may be more ecologically valid (28). Second, the BRIEF-A allows for both patient and caregiver reports and provides normed scores by age. Third, sensitivity analyses were conducted that omitted BRIEF-A items potentially related to the MND physiological disease process and adjusted for disease severity (i.e., total ALSFRS-R). In these analyses, patient-reported self-regulatory problem-solving difficulties remained a robust and statistically significant predictor of survival. Behavioral measures, such as the BRIEF-A, often include items that could inflate deficit scores due to motor impairment. Thus, future research should also be sensitive to potential motor bias when applying behavioral measures to MND. Fourth, the executive functioning test utilized in the study, the WCST, is not dependent on speed or motor function, making it particularly suitable for MND. Finally, the present study adjusted for several important prognostic indicators identified in the literature and employed

continuous predictors. Previous research has frequently categorized cognition and/or behavior variables, which reduces power and can obscure real effects.

In summary, the present research bolsters existing literature that suggests behavioral deficits are indicators of poorer prognosis in ALS (11,12,13) by extending the relationship to mild self-regulation difficulties in MND and survival. Additional research is needed to assess which behavioral aspects are most predictive of survival in ALS/MND and which assessment methods best capture these difficulties. Disease course heterogeneity continues to be a challenge in detecting treatment efficacy in ALS/MND. If these findings are replicated, patient-reported self-regulation difficulties may be a useful tool to identify patients with MND at risk for poorer prognosis.

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Acronyms

ALS	amyotrophic lateral sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
ALS-FTD	amyotrophic lateral sclerosis with coexisting frontotemporal dementia
ALS-FTD-Q	Amyotrophic Lateral Sclerosis-Frontotemporal Dementia Questionnaire
BRIEF-A	Behavior Rating Inventory of Executive Functions adult version
FTD	frontotemporal dementia
HR	hazard ratio
MND	motor neuron disease
MQOL	McGill Quality of Life Questionnaire
PLS	primary lateral sclerosis
WCST	Wisconsin Card Sorting Test

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Figure 1.

Survival predicted by patient-reported self-regulatory behavior (i.e., Behavioral Regulation subdomain; BR).

Figure shows survival curves generated by a Cox proportional hazard regression model, including disease covariates. Each dot represents the model-estimated survival for each unique event time (i.e., patient death or censoring). The BRIEF-A Behavioral Regulation subdomain reflects self-regulation as it pertains to behaviors and emotions; higher T-scores indicate more self-regulation difficulty. Continuous variables were assessed in the statistical models, though self-regulation is trichotomized for illustrative purposes. L = Low self-regulatory behavior difficulty (10 T-score points below the sample mean), M = Mean self-regulatory behavior difficulty (at the sample mean), and H = High self-regulatory behavior difficulty (10 T-score points above the sample mean).

Figure 2.

Survival predicted by patient-reported self-regulatory problem-solving (i.e., Metacognition subdomain; MC).

Figure shows survival curves generated by a Cox proportional hazard regression model, including disease covariates. Each dot represents the model-estimated survival for each unique event time (i.e., patient death or censoring). The BRIEF-A Metacognition subdomain reflects self-regulation as it pertains to problem-solving and goals; higher BRIEF-A T-scores indicate more self-regulation difficulty. Continuous variables were assessed in the statistical models, though self-regulation is trichotomized for illustrative purposes. L = Low self-regulatory problem-solving difficulty (10 T-score points below the sample mean), M = Mean self-regulatory problem-solving difficulty (at the sample mean), and H = High self-regulatory problem-solving difficulty (10 T-score points above the sample mean).

Table 1**Sample Demographics and Disease Characteristics**

Demographics	Patients Total sample	Patients Deceased sample	Patients Censored sample	Caregivers
N	37	23	14	36
Age in yrs.	59.97 (11.57)	60.91 (11.76)	58.43 (11.51)	58.33 (13.31)
Male	54.10% (<i>n</i> = 20)	56.5% (<i>n</i> = 13)	50% (<i>n</i> = 7)	27.78% (<i>n</i> = 10)
Education in yrs.	13.81 (3.73)	14.52 (4.07)	12.68 (2.87)	–
White	97.22% (<i>n</i> = 36)	95.7% (<i>n</i> = 22)	100% (<i>n</i> = 14)	97.20% (<i>n</i> = 35)
Latino	2.70% (<i>n</i> = 1)	4.3% (<i>n</i> = 1)	0% (<i>n</i> = 0)	2.78% (<i>n</i> = 1)
Disease characteristics				
ALS	83.78% (<i>n</i> = 31)	95.7% (<i>n</i> = 22)	64.3% (<i>n</i> = 9)	–
PLS	16.22% (<i>n</i> = 6)	4.3% (<i>n</i> = 1)	35.7% (<i>n</i> = 5)	–
Disease severity (ALSFRS-R total)	30.03 (8.83)	28.95 (8.10)	31.92 (10.05) [*]	–
Disease severity range	13-46	13-43	13-46 [*]	–
Limb onset	78.38% (<i>n</i> = 29)	69.6% (<i>n</i> = 16)	92.9% (<i>n</i> = 13)	–
Bulbar onset	21.62% (<i>n</i> = 8)	30.4% (<i>n</i> = 7)	7.1% (<i>n</i> = 1)	–
Non-verbal communication	18.91% (<i>n</i> = 7)	26% (<i>n</i> = 6)	7.1% (<i>n</i> = 1)	–
Any ventilation use	18.91% (<i>n</i> = 7)	21.7% (<i>n</i> = 5)	14.3% (<i>n</i> = 2)	–
Median yrs. dx to death/censoring	4.27 (4.50)	3.12 (1.72)	10.17 (3.65)	–
Median yrs. onset to death/censoring	5.48 (5.06)	4.36 (2.49)	13.21 (3.89)	–
Yrs. since dx at assessment	3.00 (2.84)	1.78 (1.16)	4.88 (3.68)	–
Yrs. since onset at assessment	4.74 (3.50)	3.12 (2.03)	7.38 (3.86)	–
Yrs. assessment to death/censoring	3.15 (2.16)	1.64 (1.15)	5.62 (0.26)	–

Note. Means and frequencies unless otherwise indicated; standard deviations are provided in parentheses. Patients deceased sample and patients censored sample represent the portions of the sample that were deceased or alive (censored for survival analysis) at the 6-year follow-up. ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale-Revised; PLS = primary lateral sclerosis;

^{*} indicates that one patient's total ALSFRS-R score was excluded.

Table 2

Self-Regulation and Executive Functioning Scores and Impairments

Scores	Patient-Reported			Caregiver-Reported		
	Total sample	Deceased sample	Censored sample	Total sample	Deceased sample	Censored sample
BRIEF-A Total T-score	58.57 (11.55)	60.78 (9.89)	54.93 (13.46)	50.81 (8.28)	51.13 (8.66)	50.23 (7.88)
Behavioral Regulation T-score (Self-regulatory behavior)	56.05 (9.76)	58.17 (10.31)	52.64 (7.81)	49.58 (7.39)	48.65 (7.49)	51.23 (7.20)
T 65	16.22% (n = 6)	26.1% (n = 6)	0% (n = 0)	5.56% (n = 2)	4.3% (n = 1)	7.69% (n = 1)
Metacognition T-score (Self-regulatory problem-solving)	57.41 (11.75)	60.96 (12.46)	51.57 (7.81)	52.08 (9.69)	53.52 (10.26)	49.54 (8.36)
T 65	18.92% (n = 7)	30.4% (n = 7)	0% (n = 0)	13.89% (n = 5)	17.4% (n = 4)	7.69% (n = 1)
WCST Perseverative Errors T-score	48.70 (8.68)	50.57 (8.12)	45.64 (8.98)	–	–	–
< 16 th percentile	16.22% (n = 6)	8.7% (n = 2)	28.6% (n = 4)	–	–	–

Note. Means and frequencies unless otherwise indicated; standard deviations are provided in parentheses. Patients deceased sample and patients censored sample represent the portions of the sample that were deceased or alive (censored for the survival analysis) at the 6-year follow-up. Caregiver-reported ratings are of patients' abilities; 75% of the patients' caregivers were a spouse living in the same household. The BRIEF-A Behavioral Regulation subdomain reflects self-regulation as it pertains to behaviors and emotions, whereas the Metacognition subdomain reflects self-regulation as it pertains to problem-solving and goals. Higher BRIEF-A T-scores indicate more self-regulation difficulty; T-scores 65 represent clinical impairment compared to age-standardized norms. Lower WCST perseverative error T-scores indicate more executive dysfunction; scores < 16th percentile represent clinical impairment compared to age and education-standardized norms; no patients scored < 5th percentile. ALS = amyotrophic lateral sclerosis; BRIEF-A = Behavior Rating Inventory of Executive Functions adult version; PLS = primary lateral sclerosis; WCST = Wisconsin Card Sorting Test.

Table 3**BRIEF-A Scores for Sensitivity Analyses Omitting Motor Items**

Variable	Patient-reported	Caregiver-reported
Behavioral Regulation raw	43.46 (8.60)	39.94 (8.54)
Metacognition raw	52.54 (10.69)	48.64 (12.38)

Note. Means; standard deviations are provided in parentheses. Higher scores indicate more self-regulation difficulty. The following items were removed from the BRIEF-A 75-item measure for sensitivity analysis in order to assess bias from items potentially related to the physiological process of MND. Inhibit subscale items: 5 and 16; Initiate subscale items: 14 and 20; Organization of Materials subscale items: 7, 40, 60, and 74. BRIEF-A = Behavior Rating Inventory of Executive Functions adult version.