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LANGUAGE DYSFUNCTION IN MOTOR NEURON DISEASE: COGNITIVE FEATURES AND SCREENING SENSITIVITY

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LANGUAGE DYSFUNCTION IN MOTOR NEURON DISEASE: COGNITIVE FEATURES AND SCREENING SENSITIVITY

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences
at the University of Kentucky

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2019

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ABSTRACT OF DISSERTATION

LANGUAGE DYSFUNCTION IN MOTOR NEURON DISEASE:
COGNITIVE FEATURES AND SCREENING SENSITIVITY

Motor neuron disease (MND) is a set of neuromuscular diseases that affect the upper and/or lower motor neurons, resulting in progressive disability. Amyotrophic lateral sclerosis (ALS) and Primary lateral sclerosis (PLS) are two forms of MND that both involve upper motor neuron degeneration, which can also accompany extra-motor changes in cognitive, behavioral, and/or emotional functioning for some individuals. Characterization of the cognitive profile of MND is still evolving, with growing interest in cognitive subtypes. The development of cognitive screens targeted to the MND cognitive profile aim to provide efficient and accurate brief assessments. However, empirical evaluation of tailored MND cognitive screens is needed for cross-validation independent of tests' original developers. The present study addresses the cognitive profile of MND and the utility of brief cognitive screens with a focus on impairments in the language domain. The two primary aims include: (1) comprehensive assessment and characterization of language dysfunction in MND, and (2) empirical evaluation of brief cognitive screens with regard to detecting language impairments.

Forty-one patients with MND (ALS $n = 36$; PLS $n = 5$) were administered a comprehensive language battery to classify cognitive impairment (MND/ALSci; Strong et al., 2017) in the language domain and/or verbal fluency. Patients also completed two tailored cognitive screens [ALS Cognitive Behavioral Screen (ALS-CBS), Edinburgh Cognitive and Behavioral ALS Screen (ECAS)] and one general screen (Montreal Cognitive Assessment; MoCA).

The current preliminary results suggest language dysfunction in MND is characterized by prominent difficulties with word retrieval (confrontation naming) and/or syntax comprehension. However, evidence of reduced word production resembling nonfluent/agrammatic aphasia was not found. In total, 19.5% of the sample met criteria for MND/ALSci in the language domain ($n = 8$, all ALS); 22.0% met criteria for MND/ALSci in the verbal fluency domain ($n = 9$). Patients were classified into three subgroups, those with broad language impairments (ALSci-L $n = 4$, 9.8%), phonemic fluency impairments (MNDci-VF $n = 5$, 12.2%), or both impairments (ALSci-L+VF $n = 4$, 9.8%).

Results also revealed existing challenges in accurately classifying patients with language dysfunction using brief cognitive screens. The ECAS Language subscore offered limited classification of broad language impairments in the present MND sample (sensitivity 50%, specificity 70%). Among the broader cognitive screens, sensitivities to language impairments were: ALS-CBS (100%), ECAS ALS-Specific Score (75%), and MoCA (71%). Convergent validity was demonstrated between outcomes on the ALS-CBS and ECAS ALS-Specific Score ($r\phi$ = .59). Discriminant validity was also demonstrated between outcomes on ALS-CBS compared to the MoCA ($r\phi$ = .11).

Future research is needed to assess whether language dysfunction reflects a distinct MND cognitive phenotype(s) and potential relationships with disease prognosis. Naming and syntax comprehension may be fruitful language screening targets for future research.

KEYWORDS: Amyotrophic Lateral Sclerosis, Motor Neuron Disease, Language, Screening, Naming, Syntax

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09/03/2019
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NOTICE

This document represents the doctoral dissertation version of this project. However, this version does not reflect the final results of this research project as additional data collection is ongoing. Future publication of the final results is planned, as well as secondary analyses.

CHAPTER 1: INTRODUCTION

1.1 Background

Efficient and accurate cognitive assessment is an important clinical issue for patients with motor neuron disease (MND). MND is a set of neuromuscular diseases defined by upper and/or lower motor neuron degeneration resulting in progressive disability. Amyotrophic lateral sclerosis (ALS), the most common form of MND, is characterized by progressive upper and lower motor neuron degeneration. Primary lateral sclerosis (PLS) is a rarer form of MND that is characterized by progressive upper motor neuron degeneration, whereas lower motor neurons remain comparatively intact. Though MND was previously thought to spare cognitive functioning, it is now recognized that impairments can develop in some people with ALS and PLS (Agarwal et al., 2018; Strong et al., 2017). It is estimated that cognitive impairments impact up to 49% of people with ALS (Phukan et al., 2012). Preliminary evidence suggests that in ALS, cognitive impairments are important prognostic indicators and may affect patients' ability to follow multidisciplinary regimens (Chiò et al., 2009; Elamin et al., 2011; Gordon et al., 2010).

Some MND clinics have limited resources for neuropsychological assessment and patient referrals may require triaging. Therefore, there is a growing need for brief, efficient, and accurate cognitive screening tools sensitive to impairments observed in MND. Responding to this demand, the development of cognitive screens tailored to MND is burgeoning (Abrahams, Newton, Niven, Foley, & Bak, 2014; Beeldman, Govaarts, et al., 2016; Woolley et al., 2010) and cognitive screening measures developed for other conditions have also been applied to patients with MND (Osborne, Sekhon,

Johnston, & Kalra, 2014; Oskarsson et al., 2010). Empirical evaluation of cognitive screens for MND is needed to provide cross-validation independent of the test's original developers.

1.2 Cognitive Screening in Motor Neuron Disease

Brief cognitive screens have produced varying results for identifying impairments in people with MND. Yet, cross-validation and accuracy evaluations for cognitive screening measures among people with MND is scarce. In general, cognitive screens applied to MND take either a tailored or broad approach, which may impact their detection accuracy for impairments in MND. Screening measures that use a tailored approach target cognitive domains thought to be cardinal to MND, namely executive functions (Abrahams et al., 2014; Beeldman, Govaarts, et al., 2016; Woolley et al., 2010). In contrast, general cognitive screening measures (e.g., Montreal Cognitive Assessment; MoCA; Nasreddine et al., 2005) that use a broad approach assess several cognitive domains, though potentially less precise for MND.

In ALS for example, the MoCA, a general cognitive screen, classified more patients as cognitively impaired than a screen focused on executive functioning, the Frontal Assessment Battery (53% and 21% impaired respectively; FAB; Dubois, Slachevsky, Litvan, & Pillon, 2000, Osborne et al., 2014). This raises the question of whether the FAB provides too narrow assessment, leaving certain impairments undetected. Perhaps broader cognitive functions assessed by the MoCA provides higher sensitivity to impairments in MND. On the other hand, the MoCA may simply result in more false-positives than the FAB, especially given its reliance on hand-motor functioning. However, conclusions about the relative accuracy of these two cognitive

screens cannot be determined from this example. Cognitive screens require validation against cognitive impairment criteria to produce operating characteristics (e.g., sensitivity, specificity), which is overlooked by some previous research (Osborne et al., 2014; Oskarsson et al., 2010).

Few MND studies evaluate cognitive screens against gold standard cognitive impairment criteria and methodologies vary widely. Cognitive impairment criterion consist of both the test battery content and performance classification. Criteria often include broad neuropsychological test batteries that assess a breadth of cognitive domains, although at the cost of depth within these domains. In some batteries, the language domain was assessed with a single test (Floris et al., 2012). In other batteries, language domain tests were restricted to abilities specifically targeted by the screen (Pinto-Grau et al., 2017). Criteria from another study included a standard cognitive battery developed for other neurological conditions (e.g., the Consortium to Establish a Registry for Alzheimer's Disease plus Scale; Lulé et al., 2015). Such batteries may variably capture domain-specific impairments critical to the MND cognitive profile. Likewise, impaired performance is diversely classified. For example, one study defined impaired performance by z-scores ≤ 2, averaged across multiple tests (Pinto-Grau et al., 2017). This method may detect global impairments but could obscure impairments from individuals with poor cognitive functioning in specific areas but strong abilities in other areas.

In sum, screening operating characteristics reflect the cognitive impairment criteria they are validated against, including the breadth or depth of those criteria and appropriateness for the patient population. Previous gold standard criterion included

batteries with limited assessment of the language domain and few classified impairments using the consensus criteria for the diagnosis of frontotemporal dysfunction in ALS/MND (Strong et al., 2009; Strong et al., 2017; Woolley et al., 2010).

1.3 Broad Cognitive Assessment Issues in Motor Neuron Disease

Within this nascent field several broader assessment challenges remain, affecting the cognitive impairment criteria that screening measures are validated against. Since MND was established as a spectrum disorder that affects cognition, efforts to characterize impairment patterns have increased, though the MND cognitive profile is still evolving (Beeldman, Raaphorst, et al., 2016; Raaphorst, de Visser, Linssen, de Haan, & Schmand, 2010). Early on, executive dysfunction received substantial recognition and was central to the original consensus criteria for cognitive and behavioral syndromes in ALS (Strong et al., 2009). More recently, a meta-analysis revealed impairments in several other cognitive domains in ALS including language, verbal fluency, verbal memory, and social cognition, in addition to executive dysfunction (Beeldman, Raaphorst, et al., 2016). Revisions to the consensus criteria now recognize the involvement of other cognitive domains, particularly language and social cognition impairments (Strong et al., 2017).

However, optimal neuropsychological assessment methods for MND remain unclear. The National Institute for Health and Care Excellence (NICE) released assessment guidelines for MND, though the authors indicated that these guidelines were constructed via expert informal consensus due to current lack of clinical evidence (NICE, 2016). The NICE guidelines highlight a variety of cognitive measures that may be used in MND, with no clear agreement on validated assessment tools. The updated Strong and colleagues (2017) criteria began to address the need for consensus on assessment tools

for MND, though evidence for some cognitive measures is limited. Certain measures provide limited psychometric information or demonstrate poor properties, particularly language tests. Additional research is needed to establish the nature of language impairments in MND and measures with good psychometric properties that capture these impairments.

There is also growing interest in cognitive profiles and potential MND subtypes. Varied cognitive impairments may represent different MND manifestations, and thus research on deficits beyond executive dysfunction may help elucidate MND cognitive phenotypes (Consonni et al., 2016; Taylor et al., 2013). For example, frontotemporal dementia (FTD), a nosologically related condition, has multiple variants with some patients exhibiting greater executive dysfunction and others exhibiting greater language dysfunction (Neary et al., 1998). It is plausible that MND may have similar subtypes that manifest different deficit proportions across cognitive domains.

Thus, for brief cognitive screening effectiveness within the MND population, these tools need to detect patients with cognitive impairments beyond executive dysfunction alone. Cognitive screening in MND may require a balance between targeted and broad assessment, which both have strengths and weaknesses. In MND, targeted cognitive screens may be highly sensitive to executive dysfunction but may lack sensitivity to other commonly impaired cognitive domains such as language dysfunction. In contrast, broad cognitive screens may sample several cognitive domains but may not provide adequate sensitivity to distinct cognitive impairments that manifest in MND.

1.4 Language Dysfunction in Motor Neuron Disease

The current study focuses on cognitive abilities in the language domain as cognitive impairment criteria. This study takes a 'clinical-neuroanatomical approach' to language assessment (Spreen & Risser, 2003). As previously mentioned, executive dysfunction is well established in MND, though language dysfunction has received less attention. Assessment of both executive and language dysfunction is vital in MND as "predominantly dysexecutive" and "predominantly linguistic" cognitive profiles have been proposed (Taylor et al., 2013, p. 497). Next, language abilities are discussed, followed by domain interrelationships with executive abilities.

Language is a complex system of hierarchical abilities including several basic (e.g., phoneme perception, symbol decoding) and complex functions (e.g., grammar, verbal concept integration) (Hickok & Poeppel, 2007). Generally speaking, language abilities may be partitioned into expressive and receptive functions, which rely on associative networks heavily implicated in the frontal and temporal lobes, but not exclusively. The term aphasia refers to a diverse set of language impairment syndromes. Aphasias can arise from neurological insult (e.g., stroke) or progressive neurodegeneration such as frontotemporal lobar degeneration. The historic Wernicke-Lichtheim Model classifies language dysfunction in terms of several classic syndromes (e.g., Wernicke's aphasia, Broca's aphasia, transcortical sensory aphasia, transcortical motor aphasia, conduction aphasia; Graves, 1997), although contemporary cognitive research indicates this model is underspecified (Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Dronkers, Ivanova, & Baldo, 2017; Hickok & Poeppel, 2007).

Language abilities are multidimensional and comprehensive assessment should include perception, comprehension, expression, and responses to various language-based stimuli (Lezak, Howieson, Bigler, & Tranel, 2012). The Gorno-Tempini and colleagues (2011) criteria recommend several language tasks for the assessment of progressive degenerative aphasias including measures of speech production, confrontation naming, repetition, comprehension, semantic knowledge, reading, and spelling.

Several expressive and receptive language deficits have been identified among patients with MND, though evidence is conflicting. It is unclear which language abilities are primarily affected in MND. Table 1 summarizes previous language research, with some research suggesting deficits in MND and contrary research suggesting intact language functioning. This summary table is not exhaustive but provides a broad overview (for a recent systematic review also see Pinto-Grau, Hardiman, & Pender, 2018). A meta-analytic review indicates that language deficits have the largest effect size for patients with ALS in comparison to healthy controls (g = .56), primarily driven by confrontation naming (g = 0.60; Beeldman, Raaphorst, et al., 2016). However, complications exist, impaired confrontation naming can reflect several underlying problems such as an expressive language deficit, semantic deficit, perceptual deficit, or potential interference from executive dysfunction (Migliaccio et al., 2016). The need for detailed and systematic language assessments in MND has been recognized (Bak & Hodges, 2004; Strong, Grace, Orange, & Leeper, 1996; Tsermentseli et al., 2016), which may have implications for both understanding the disease process and clinical care.

Table 1. *Summary of Previous MND Research Suggesting Language Deficits or Intact Functioning*

Function(s)	Task	Supportive evidence of language deficits	Contrary evidence of intact functioning
Verbal Command Execution	Modified token test	Tsermentseli et al., 2016*	
	Token Test short form	Talbot et al., 1995*	Bambini et al., 2016
Confrontation Naming	Boston Naming Test	Libon et al., 2012; Massman et al., 1996; Taylor et al., 2013*; York et al., 2014*	Ash et al., 2014; Talbot et al., 1995
	Category Specific Names Test	Taylor et al., 2013*	
	HSB Naming		Rakowicz & Hodges, 1998
	SYDBAT Naming	Leslie et al., 2015*	
	ACE-R Naming	Leslie et al., 2015*	
	Graded Naming Test	Abrahams et al., 2004*; Cobble, 1998*	Abrahams et al., 2000; Rakowicz & Hodges, 1998; Tsermentseli et al., 2016
	Novel noun naming task		Papeo et al., 2015
Verb Naming	Action Naming Test		Libon et al., 2012
	Novel action naming task		Papeo et al., 2015
Receptive Vocabulary	British Picture Vocabulary Test	Taylor et al., 2013*	Tsermentseli et al., 2016
Semantic Processing	Pyramids and Palm Trees Test	Rakowicz & Hodges, 1998*; Libon et al., 2012	Taylor et al., 2013; Tsermentseli et al., 2016; York et al., 2014
	SYDBAT Semantic Associations and Word Comprehension subtests		Leslie et al., 2015
	ACE-R Auditory sentence-picture matching	Leslie et al., 2015*	
	HSB Word-Picture Matching		Rakowicz & Hodges, 1998
	PALPA Word Semantic Association test		Cobble, 1998
	Novel Associativity Judgment task (nouns)		York et al., 2014
	Novel noun word-picture matching task		Papeo et al., 2015
Verb Processing	Kissing and Dancing Test	Taylor et al., 2013*; Tsermentseli et al., 2016*	
	Novel Associativity Judgment task (verbs)	York et al., 2014*	
	Novel verb word-picture matching task		Papeo et al., 2015
Verb Sequencing	Novel picture sequencing task	Talbot et al., 1995*	
	Novel sentence and picture sequencing task	Papeo et al., 2015*	
Synonyms Judgment	PALPA Judgment of Synonyms	Taylor et al., 2013*	Cobble, 1998

Table 1. (Continued)			
Receptive Grammar/Syntax	TROG	Rakowicz & Hodges, 1998*; Taylor et al., 2013*; Tsermentseli et al., 2016*	
	TROG abbreviated		Kamminga et al., 2016
	Novel Grammatical Comprehension task		York et al., 2014
	PALPA Auditory sentence to picture matching	Cobble, 1998*	
	STA	Yoshizawa et al., 2014	
Expressive Grammar/Syntax	Frog, Where Are You? (Sentence-level fluency, grammar, lexical access)	Ash et al., 2015*	
Narrative Discourse	Frog, Where Are You? (Speech connectedness)	Ash et al., 2014*	
	QPA using the BDAE Cookie Theft picture description	Tsermentseli et al., 2016*	
	BDAE Cookie Theft picture description complexity index		Taylor et al., 2013
Pragmatics Expressive & Receptive	Novel test battery, APACS	Bambini et al., 2016*	
Spelling	Graded Difficulty Spelling Test	Taylor et al., 2013*	
	PALPA Spelling to dictation	Cobble, 1998*	
Phonemic Fluency	Controlled Oral Word Association Test (FAS)	Ash et al., 2014*; Massman et al., 1996; Rakowicz & Hodges, 1998*; York et al., 2014*	Libon et al., 2012; Talbot et al., 1995
	Vfi (CFL)		Jelsone-Swain et al., 2015
	Vfi (S)	Taylor et al., 2013*	Tsermentseli et al., 2016
	Vfi (PRW)	Abrahams et al., 2004*	Abrahams et al., 2000
	Written *vfi* (S)	Abrahams et al., 2004*	Abrahams et al., 2000
Semantic Fluency	Animal fluency	York et al., 2014*	Ash et al., 2014
	HSB Category Fluency (various)	Rakowicz & Hodges, 1998*	
	Vfi (Animals, foods)		Taylor et al., 2013; Tsermentseli et al., 2016
	Vfi (Animals)	Abrahams et al., 2000*	Abrahams et al., 2004
	Vfi (Colors, fruits, towns)		Abrahams et al., 2000; Abrahams et al., 2004
Combined Fluency	ACE-R Fluency (Letter P, Animals)	Leslie et al., 2015*	Kamminga et al., 2016
Lexical Decisions/ Est. Verbal IQ	Spot the Word Test	Taylor et al., 2013*	

Table 1. (Continued)			
Word Reading/ Est. Verbal IQ	NART		Abrahams et al., 2000; Cobble, 1998; Rakowicz & Hodges, 1998; Talbot et al., 1995
	ANART		Massman et al., 1996
Note. ACE-R = Addenbrooke's Cognitive Examination-Revised; ANART = American version of the National Adult Reading Test; APACS = Assessment of Pragmatic Abilities and Cognitive Substrates, a novel test battery that includes expressive and receptive tasks including Interview, Description, Narratives, Humor, and Figurative Language tasks; BDAE = Boston Diagnostic Aphasia Examination; HSB = Hodges' semantic battery per Hodges, Salmon, & Butters (1991); NART = National Adult Reading Test; PALPA = Psycholinguistic Assessment of Language Processing in Aphasia; STA = Syntax Test for Aphasia; SYDBAT = Sydney Language Battery; TROG = Test of Receptive Grammar; *Vfi* = Verbal Fluency Index, which adjusts for motor speed per Abrahams et al., 2000; QPA = Quantitative Production Analysis. * Indicates statistically significant difference compared to a control group.			

Furthermore, cognitive abilities within the language and executive functioning domains are intertwined. The frontal lobe and its interconnections support executive functioning, language output, and motor functions, all implicated in MND. Complex language functions such as syntax/grammar and verb processing are thought to somewhat depend on executive functioning and prefrontal regions including the dorsolateral prefrontal cortex (Grossman et al., 2008; Novais-Santos et al., 2007). Executive abilities also depend on intact basic functions, such as language (Miyake et al., 2000). Language and executive dysfunction are linked in MND; executive functioning accounted for 44% of the variance in language abilities in patients with ALS (Taylor et al, 2013). Verbal fluency tasks in particular, demonstrate these interrelated abilities, as this paradigm is both executive and linguistic in nature. Broadly, verbal fluency tasks require expressive language abilities, psychomotor speed, lexical dependent retrieval, semantic dependent retrieval, executive dependent retrieval and components such as initiation, productivity, monitoring, and updating (Lezak et al., 2012; Shao, Janse, Visser, & Meyer, 2014). For patients with ALS, worse phonemic fluency was associated with impaired fMRI activation within extensive brain regions suggestive of both executive and language components (Abrahams et al., 2004). Yet, patients with normal executive performance

can exhibit language dysfunction suggesting that despite overlap, executive and language abilities may be discriminable in MND (Tsermentseli et al., 2016). Others suggest that certain language impairments in ALS, such as syntax/grammar processing, reflect problems with sequencing and organization that are executive in nature (Papeo et al., 2015).

In sum, although language and executive functioning are considered distinct cognitive domains, and at times may be examined separately, it is not possible at present to completely disentangle these domains in MND. Nevertheless, the scope of brief cognitive screening measures may impact their sensitivity to various cognitive impairments in MND. Certain cognitive impairments, such as executive dysfunction, may be more readily detected than others, such as language dysfunction.

1.5 The Current Study

The overarching purpose of the current study is to collect information that may improve cognitive assessment for patients with MND, which have important clinical implications. The first goal is to comprehensively assess language dysfunction in MND to elucidate cognitive features and replicate previous research.

The second goal is to empirically evaluate brief cognitive screens for sensitivity to language impairments in MND and provide cross-validation independent of the tests' original developers. Three brief cognitive screens are examined against gold standard language criteria. These include a comprehensive language battery and the Strong and colleagues (2017) consensus criteria for MND/ALS with cognitive impairment. Specific study aims include:

1.5.1 Primary aims.

Aim 1. Examine the pattern of language dysfunction in patients with MND.

Hypothesis 1: Language impairments in MND will resemble that of nonfluent/agrammatic aphasia (i.e., prominent word production and syntax impairments) per the Gorno-Tempini and colleagues (2011) criteria, potentially suggestive of fronto-insular degeneration.

Aim 2. Empirical evaluation of brief cognitive screens applied to the MND population, in particular, the relative sensitivity of three brief cognitive screens for detecting language impairments in MND and the relationships among these measures. The goal of these direct comparison is to inform future assessment methods.

Hypothesis 2a: It was hypothesized that screening measures tailored to MND [i.e., Edinburgh Cognitive and Behavioral ALS Screen (ECAS; Abrahams et al., 2014) and ALS Cognitive Behavioral Screen (ALS-CBS; Wooley et al., 2010)] would demonstrate significantly higher sensitivity to language impairments in MND. In contrast, the MoCA, a general cognitive screening measure, would demonstrate lower sensitivity to language impairments in MND. This result would provide evidence of discriminant validity for the tailored screening measures and support for their use in MND.

Hypothesis 2b: Given that the ECAS includes a targeted language assessment, it was hypothesized that the ECAS Language subscore would demonstrate the highest sensitivity to language impairments, as compared to the ALS-CBS and MoCA due to the scope of these measures.

Hypothesis 2c: If tailored MND cognitive screens index a common construct (i.e., the MND cognitive profile), convergent measures should exhibit higher intercorrelations (i.e., the ALS-CBS Total Score correlated with the ECAS ALS-Specific Score) and divergent measures should exhibit lower intercorrelations (i.e., the ALS-CBS and ECAS correlated with the MoCA, a general screening measure).

1.5.2 Exploratory aim.

Aim 3. Assess various screening combinations to examine whether higher sensitivity to language impairments in MND is achieved.

CHAPTER 2: METHODS

2.1 Participants

2.1.1 *A priori* power analyses.

Two *a priori* methods informed the minimum patient sample size target for this project. The first *a priori* power analysis focused on effect sizes for language dysfunction in ALS/MND. This power analysis indicated that at 80% power ($p < .05$), 41 individuals with MND would be sufficient to detect a large effect for language dysfunction based on a previous meta-analysis in ALS (language domain $g = 0.56$; confrontation naming $g = 0.60$; phonemic fluency $g = 0.68$; Beeldman, Raaphorst, et al., 2016*;* Faul, Erdfelder, Lang, & Buchner, 2007).

The second method focused on sample size for sensitivity and specificity analyses (Bujang & Adnan, 2016). Within this framework, screening evaluations aimed to assess the sensitivities of three brief cognitive screens for detecting language impairments in patients with MND. It was predicted that the prevalence of language impairments would fall between 40% and 50% (Taylor et al., 2013). Based on 40% estimated prevalence, a minimum sample size of 50 patients with MND (including 20 with language impairments) would be required to achieve a minimum power of 80% (actual power = 80.4%) for detecting a change in the sensitivity of a screening measure from .50 to .80, with a target significance level of $p < .05$ (actual $p = .041$; Bujang & Adnan, 2016). Based on 50% estimated prevalence, a minimum sample size of 40 patients with MND (including 20 with language impairments) would be required to achieve a minimum power of 80% for screening sensitivity, using the same parameters above. These minimum sample sizes also exceed the estimates to achieve a minimum power of 80% for

screening specificity. Considering all methods outlined above, the *a priori* minimum patient sample size target was set to $N = 41$. This minimum target was met, though additional data collection continues. It is necessary to address that the observed prevalence of language impairments was lower than *a priori* predictions. *Post hoc* power for the sensitivity and specificity analyses is discussed in the *Limitations* section.

2.1.2 Patient sample.

Patients were eligible for participation if they were classified by their neurologist as having ALS or PLS (Brooks, Miller, Swash, & Munsat, 2000; Pringle et al., 1992), both requiring progressive upper motor neuron degeneration. Additional inclusion criteria for patients were: age between 18 and 97 years, fluency in English, diagnosis >1 month prior to participation, absence of a learning or intellectual disability or language impairment (e.g., dyslexia), absence of serious mental illness (e.g., schizophrenia spectrum disorders, psychosis, bipolar disorder, PTSD with current flashbacks and/or hyperarousal, current substance abuse disorder, or active suicidal ideation), and absence of other major health conditions that could affect cognition [e.g., stroke, epilepsy disorder, organ failure, hydrocephalus, brain tumor, complicated mild traumatic brain injury (TBI) with skull fracture, or moderate to severe TBI (i.e., post-traumatic amnesia > 24 hrs, loss of consciousness > 30 mins; Lezak et al., 2012)].

During the initial recruitment period, 62 individuals with MND were screened for the study. Although this study was broadly inclusive, 5 individuals (8.1%) were unable to participate due to advanced illness (e.g., frequent hospitalizations, unable to communicate) and 3 individuals (4.8%) passed away before they could take part in the study. An additional 13 individuals (20.9%) were ineligible for the following reasons

(*note:* groups not mutually exclusive): history of learning disability (*n* = 3), known dyslexia (*n* = 4), suspected dyslexia (*n* = 3; i.e., reported trouble learning to read/write), special education (*n* = 2), moderate to severe TBI (*n* = 3), epilepsy disorder (*n* = 1), advanced stage organ failure (*n* = 1), and PTSD with current flashbacks (*n* = 1).

The resulting patient sample included in these preliminary results consisted of 41 individuals with MND (PLS *n* = 5; classic ALS *n* = 35; adult with juvenile onset ALS *n* = 1) residing in the Ohio River Valley region of the U.S. (Kentucky *n* = 33; Ohio *n* = 5; West Virginia *n* = 2; Tennessee *n* = 1). Participants were recruited via research flyers distributed within the ALS/MND clinic at the University of Kentucky (*n* = 31) and local ALS support groups (*n* =10).

2.1.3 Control sample.

Healthy family members/caregivers were invited to participate as controls for two cognitive tasks (i.e., the Kissing and Dancing Test, KDT, and spoken verbal fluency index, *vfi*; Abrahams et al., 2000; Bak & Hodges, 2003) due to limited availability of standardization data for these tasks. Parallel to the patient sample, inclusion criteria were: age between 18 and 97 years, fluency in English, absence of a learning or intellectual disability or language impairment, absence of serious mental illness, and absence of other major health conditions that could affect cognition. Blood relatives of patients with known or suspected familial MND were also excluded.

Fourteen patients did not have a family member/caregiver that was willing/able to participate. Two family members/caregivers chose not to complete the cognitive tasks but took part in a psychosocial evaluation for secondary research projects. Two additional family members/caregivers agreed to complete the KDT but chose not to complete the *vfi*

tasks. Family members/caregivers were excluded as healthy controls for due to the following reasons: blood relative of patient with known or suspected familial MND (n = 2), severe mental illness (n = 1). The resulting healthy control sample included in these preliminary results consisted of 22 individuals (KDT n = 22; *vfi* n = 20). See Table 2 for demographics.

Table 2. *Sample Demographics and Background Characteristics*

	Patients	Controls
N	41	22
Age *M* (*SD*)	60.98 (11.09)	56.82 (13.99)
Education yrs. *M* (*SD*)	14.24 (2.46)	14.55 (2.28)
Estimated FSIQ *M* (*SD*)	109.00 (7.18)	109.80 (5.67)
Right handed	34 (82.9%)	--
Left handed	7 (17.1%)	--
Male	26 (63.4%)	5 (22.7%)
Female	15 (36.6%)	17 (77.3%)
White/Caucasian	38 (92.8%)	21 (95.5%)
Black/African American	1 (2.4%)	0 (0%)
Hispanic/Latinx	1 (2.4%)	0 (0%)
Asian American	0 (0%)	1 (4.5%)
Other race/ethnicity	1 (2.4%)	0 (0%)

Note. Frequencies and percentages unless otherwise indicated. Estimated FSIQ = full scale IQ estimated from the Barona demographics formula (Barona, Reynolds, & Chastain, 1984).

2.2 Data Collection Procedure

Eligible patients had the opportunity to attend a research visit at the University of Kentucky or in their home, to ease travel burden and allow patients with advanced illness to participate. All patients opted for a home visit. Informed consent was obtained from all participants, patients also completed the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC; Jeste et al., 2007). All research visits were conducted by the author (NEGW), a clinical neuropsychology doctoral candidate. Study

procedures took approximately 2.5 hours for patients and 1 hour for family members/caregivers. Patients were compensated $20 cash for their time. Controls were not compensated. The University of Kentucky Institutional Review Board approved all study procedures.

2.2.1 Patient data collection.

For patients, the study procedures included two parts: (1) collection of demographic information, questionnaires, and administration of three brief cognitive screens, and (2) a comprehensive language battery. For part one, patients and family members/caregivers were interviewed together (if applicable) regarding the patient's medical history and physical symptoms (e.g., disease onset, functional abilities). Next, patients were interviewed individually about their psychological functioning and were administered a series of three brief cognitive screens, in a counter-balanced order to control for order effects. For part two of the study, patients were administered a comprehensive language battery. Verbal fluency measures were administered first to prevent performance interference from the other language tests. The other cognitive tests were administered using two orders (opposite order for even and odd IDs) to minimize potential fatigue effects for tests administered later in the battery. Patients were provided breaks throughout the assessment.

Testing accommodations. At the beginning of the research visit patients indicated their preferred communication method (spoken responses $n = 38$; written responses $n = 3$) and completed most study procedures using this method. A flexible testing approach was used based on each patients' particular physical abilities and limitations (see Table 3). Patients with severe dysarthria or hand weakness completed substitute tests (e.g., written

instead of spoken picture description to assess word production). In some cases, certain tasks were omitted due to lack of a substitute test (e.g., repetition). However, 87.8% (n = 36) of the sample completed all tasks. Measures that do not require quick motor or verbal responses were intentionally favored due to potential physical limitations of patients. However, when applicable, adjustments for speed were applied (e.g., *vfi*) as described in the measures section. All questionnaires were read to patients by the examiner. Response cards were presented that displayed the rating scale for each questionnaire. Patients provided either spoken responses or pointed to their rating on the response card. Similarly, for many test items patients provided spoken responses (e.g., "picture in the top right corner") or pointed to their response. For yes/no items, patients that were unable to speak were provided a response card to point to their answer.

Table 3. *Flexible Battery used to Accommodate Motor/Speech Impairments*

Function/Ability	Standard Task	Alternate Task
Brief Cognitive Screening	MoCA	MoCA-BLIND
	ALS-CBS	--
	ECAS	--
Verbal Fluency	D-KEFS Verbal Fluency *vfi*	Thurstone Written Word Fluency Test
Word Production	NAB Oral Production	NAB Writing
Following Commands	MAE-3 Token Test	NAB Auditory Comprehension Colors/Shapes/Numbers
Confrontation Naming	NAB Naming	--
Verb Processing	Kissing and Dancing Test	--
Complex Auditory Comprehension	BDAE-3 Complex Ideational Material	--
Syntax Comprehension	BDAE-3 Syntactic Processing	--
Reading Comprehension	BDAE-3 Sentences & Paragraphs	--
Repetition	BDAE-3 Word Repetition	--
Spelling	MAE-3 Spelling Test	--

Note. MoCA = Montreal Cognitive Assessment Standard Form 7.1; MoCA-BLIND = adapted version developed for individuals who are visually impaired and omits visually presented items including the motor items (visuospatial/executive abilities and naming omitted; Wittich et al., 2010); ALS-CBS = ALS Cognitive Behavioral Screen Cognitive Score; ECAS = Edinburgh Cognitive and Behavioral ALS Screen Cognitive Score; D-KEFS Verbal Fluency = Delis-Kaplan Executive Function System Verbal Fluency Tests; *vfi* = Verbal Fluency Index, which adjusts for speech speed (60 secs – secs to read words / correct words produced; Abrahams et al., 2000); NAB = Neuropsychological Assessment Battery; BDAE-3= Boston Diagnostic Aphasia Examination Third Edition; MAE-3 = Multilingual Aphasia Examination Third Edition.

Medical records review. After patients signed the consent/HIPAA authorization form, disease information (e.g., date of diagnosis) was verified from patients' medical records and additional pertinent medical information was obtained (e.g., ALS Functional Rating Scale-Revised ratings, breathing tests) per the informed consent.

2.2.2 Control data collection.

In a separate room, family members/caregivers completed questionnaires about their own demographics and medical history to determine eligibility as healthy controls. Next, eligible family members/caregivers were administered the spoken *vfi* and KDT to collect local standardization data. Family members/caregivers completed additional questionnaires about their own psychosocial functioning and provided information about the patient's emotional, behavioral, and cognitive functioning for secondary research projects.

2.3 Assessment Construction and Description

The present study aimed to characterize language abilities that may deteriorate due to extra-motor degeneration and abilities that remain intact, using objective standardized measures. The present battery was constructed with the intention of capturing a fairly comprehensive picture of language functioning among patients with MND; this includes non-aphasic patients with milder language deficits and the potential for some patients to develop aphasia comorbidity. Several factors guided test selection including recommendations for comprehensive language assessments (Gorno-Tempini et al., 2011; Lezak et al., 2012), language abilities and measures identified in the MND literature, test appropriateness for the MND population, and psychometric properties. Although qualitative and experimental paradigms can provide useful information, the

present assessment focused on objective measures with concrete scoring and standardization data for replicability in clinical practice and research. Considering these factors, the comprehensive language battery includes select subtests from three language batteries, the Boston Diagnostic Aphasia Examination Third Edition (BDAE-3; Goodglass, Kaplan, & Barresi, 2001), the Neuropsychological Assessment Battery Language Module (NAB; Stern & White, 2003), and the Multilingual Aphasia Examination Third Edition (MAE-3; Benton, Hamsher, & Sivan, 1994), along with a few supplemental tasks. Local standardization data was collected for two tasks.

The BDAE-3 and its predecessors have a long history and are among the most prominent aphasia batteries used by neuropsychologists and speech-language pathologists. The BDAE-3 is designed to aid diagnosis of classic aphasia syndromes, providing language assessment breadth and severity (Strauss, Sherman, & Spreen, 2006). The NAB is a contemporary battery with several subtests modeled after classic test paradigms. The NAB demonstrates comparatively strong psychometrics and extensive standardization data (N = 1,448 healthy adults, demographically standardized). The NAB Language Module was validated in an aphasia sample and demonstrated convergent validity with the Boston Naming Test (r = .83) and the Token Test (r = .92; Stern & White, 2003). The MAE-3 is another common aphasia battery, which allows multimodal responses for certain subtests (e.g., spoken, written, or block letter spelling) and provides a moderate-length Token Test, sensitive to language dysfunction (Benton et al., 1994; Spreen & Risser, 2003).

2.3.1 Unique psychometric issues for language tests.

Tests used to assess language functioning often exhibit psychometric properties unique from most other cognitive domains. These unique psychometric properties have important implications for the type of *standardization data* (i.e., 'norms') used to convert a person's raw score to a meaningful value that represents a comparison with a reference group (i.e., standardization sample). The converted score, or *standardized score*, is typically used to classify impaired test performance.

For many cognitive domains, test performance varies widely among healthy adults and produces a normal distribution. In contrast, language is a domain that includes several rudimentary tasks that evaluate the integrity of the language system. For illustrative purposes, a broad distinction can be made regarding the difficulty of language tests including those that assess: (1) basic and distinct language abilities and (2) complex language abilities (*note:* in actuality, these distinctions are not dichotomous but exist on a continuum).

Most language abilities assessed by aphasia batteries are best understood in the context of the first distinction above. These tasks generally aim to examine basic language functions in a fairly 'isolated' manner (e.g., repeating words or phrases, spelling simple words; Goodglass et al., 2001; Lezak et al., 2012; Spreen & Risser, 2003). These basic language tests allow for more granularity to detect mild to severe levels of aphasia, though near perfect performance is expected for 'healthy' individuals, including children. As a result, tests that assess basic language abilities produce highly skewed distributions, truncated ranges, and ceiling effects in healthy populations (Lezak et al., 2012; Sherman, Iverson, Slick, & Strauss, 2011; Spreen & Risser, 2003). Due to the purpose of these

tests, most aphasia batteries provide clinical comparison data from an aphasia standardization sample, which indicate how a person's performance compares to patients with known language dysfunction (Mitrushina, Boone, Razani, & D'Elia, 2005; Spreen & Risser, 2003). This is in contrast to standardization data from a healthy sample (or 'normative data'). Though ideally tests provide information about performance from both aphasic and healthy samples.

These properties have additional implications for test interpretation and reliability. For instance, z-scores obtained from skewed distributions do not correspond to expected percentile values as they do for normally distributed data. Percentiles must be derived directly from the standardization sample rank rather than translated from one metric to another (Sherman et al., 2011; Strauss et al., 2006). Reliability can also be limited by common language assessment characteristics. For basic language tests, internal consistency is typically stronger in clinical samples due to truncated ranges obtained by healthy samples. However, test-retest estimates from aphasia samples can be impacted by change in the condition itself, especially for aphasias from neurological insult (e.g., stroke; Spreen & Risser, 2003).

In contrast, other language tests assess more complex abilities (e.g., verbal fluency) that are best understood in the context of the second distinction above. These complex language abilities often implicate higher-level cognitive functions such as executive functioning or verbal reasoning. Complex language tasks may detect subtle language dysfunction in non-aphasic patients, though these tests are also more vulnerable to impairments in other cognitive domains and global impairment (Spreen & Risser, 2003). As a result, tests that assess complex language abilities typically produce normal

distributions in healthy populations. Such tests typically provide data from a healthy standardization sample for comparison (or 'normative data'), which is a familiar format used for most cognitive tests in other domains (e.g., intelligence, executive functioning, memory).

2.3.2 Defining impairment: Individual test level.

For the present language battery, impairments on individual tests were defined with consideration to psychometric properties, standardization data, guidelines from test manuals and the broader literature, and the Strong and colleagues (2017) consensus criteria. These criteria specify that, "impairment on individual measures is defined as a score falling at or below the 5th percentile, compared to age- and education matched norms" (Strong et al., 2017, p. 164). However, this portion of the Strong and colleagues (2017) criteria are most applicable to cognitive tests with standardization data from healthy populations.

In contrast, this cut-off is not applicable for defining impairment on cognitive tests with standardization data from clinical populations. For example, BDAE-3 standardized scores are expressed in percentiles (0 to 100th percentile, in units of 10) that compare performance to an aphasia standardization sample (Goodglass et al., 2001). In this context, a score corresponding to the 10th percentile indicates that a person's performance is better than or equal to 10% *of people with aphasia* that comprise the standardization sample, and likewise indicates their performance is worse than 90% of people in the aphasia standardization sample. However, a score this low is typically not represented in a healthy sample, suggesting extreme impairment. Accordingly, the Strong

and colleagues (2017) criteria were slightly modified within the present study to accommodate tests with aphasia standardization data.

For complex language tests with standardization data from healthy samples, scores falling at or below the 5th percentile of the healthy standardization sample were classified as impaired per Strong and colleagues (2017). This impairment cut-off approach (≤ 5th percentile) was applied to the following tests: D-KEFS Verbal Fluency (converted to spoken *vfi*; ≤ 5th percentile local norms), Thurstone Written Word Fluency Test, BDAE-3 Complex Ideational Material (T-scores ≤ 34; Heaton, Miller, Taylor, & Grant, 2004), MAE-3 Token Test (≤ 5th percentile; Benton et al., 1994), and MAE-3 Spelling Test (< 6th percentile; Benton et al., 1994).

Basic language abilities assessed by other BDAE-3 subtests provide standardization data from an aphasia sample with known language dysfunction. For most BDAE-3 subtests, scores falling at or below the 50th percentile of the aphasia standardization sample were classified as impaired. Scores within this range reflect test performance worse than or equal to 50% of the aphasia standardization sample. Notably, scores at or below the 50th percentile corresponded to Aphasia Severity Ratings ≤ 2 in the standardization sample. Language functioning at Aphasia Severity Ratings of 2 are described as "conversation about familiar subjects is possible with help from the listener. There are frequent failures to convey the idea, but the patient shares the burden of communication" (Goodglass et al., 2001, booklet p. 8). This impairment cut-off approach (≤ 50th percentile) was applied to the Syntactic Processing subtests (Touching A with B, Reversible Possessives, Embedded Sentences) and the Reading Comprehension Sentences & Paragraphs subtest. The one exception is for BDAE-3Word Repetition, the

most rudimentary language ability assessed. Healthy individuals are expected to obtain a perfect score on word repetition. Therefore, scores falling below the maximum were classified as impaired (i.e., < 10; Goodglass et al., 2001).

2.3.3 Defining impairment: Diagnostic level.

Next, patients that met diagnostic criteria for cognitive impairment (MND/ALSci; Strong et al., 2017) in the language domain or verbal fluency were classified accordingly. Strong and colleagues (2017) specify that, "language impairment is defined as: impairment on two non-overlapping tests and in which language impairment is not solely explained by verbal fluency deficits." (p. 162). Furthermore, these criteria specify that individuals with impaired phonemic fluency are classified with executive impairment (Strong et al., 2017).

Three subgroups emerged from patients that met these criteria. For the first subgroup, the term *MND/ALSci-VF* is used to refer to patients that demonstrated verbal fluency impairments (written fluency or ≥ 2 phonemic *vfi* trials). For the second subgroup, the term *MND/ALSci-L* refers to patients that demonstrated impairments on ≥ 2 tasks from the comprehensive language battery. For the third subgroup, the term *MND/ALSci-L+VF* refers to patients that met both criteria (impairments on ≥ 2 language tasks *and* written fluency or ≥ 2 phonemic *vfi* trials).

2.4 Measures

2.4.1 Descriptive measures.

Capacity to consent. Patients were administered the UBACC (Jeste et al., 2007), a 10-item practical measure that asks brief questions about the study to assess decision-making capacity. Patients were given a copy of the consent form and were not required to

rely solely on their ability to memorize the protocol details when giving consent. If patients were unable to demonstrate capacity to consent, they would not be enrolled.

Demographics. Demographic information including age, date of birth, sex, race/ethnicity, relationship between patient and caregiver (e.g., spouse, sibling), family income level, educational and occupational history.

Medical history. Medical history included physical and mental health conditions and medications that may influence performance on cognitive tasks. Information from family members/caregivers was used to determine whether they qualified as healthy controls for standardization data. Patients provided information about their MND diagnosis (e.g., date of diagnosis, symptom onset, use of supportive treatments). When available, information was verified from patients' medical records for descriptive and control purposes per the informed consent.

Estimated premorbid intelligence. The Barona formula was utilized to estimate participant's premorbid intelligence based on their demographic characteristics (Barona, Reynolds, & Chastain, 1984). The Barona formula is a regression equation developed to estimate IQ scores on the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) from examinees age, education, race, sex, occupation, and geographic location (Smith-Seemiller, Franzen, Burgess, & Prieto, 1997). This method was chosen instead of a word-reading task as such measures can result in biased estimates for individuals with language dysfunction (Lezak et al., 2012; Strauss et al., 2006). The standard error of the estimate of WAIS-R full scale IQ is 12.14, $r = .60$ (Barona et al., 1984).

Disease severity. The ALS Functional Rating Scale-Revised (ALSFRS-R; Cedarbaum et al., 1999) is a 12-item scale used to assess disease severity for people with MND via their functional abilities (i.e., speech, salivation, swallowing, handwriting, utensil use, dressing and hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and need for ventilator support). Functional abilities are individually rated from 0 to 4; total scores range from 0 (worst functional ability) to 48 (intact functional ability).

Daytime somnolence. The Epworth Sleepiness Scale (ESS; Johns, 1991) is an 8-item self-report scale that was used to assess daytime somnolence potentially related to respiratory dysfunction, which may affect cognitive performance. Items are rated from 0 (would never doze or sleep) to 3 (high chance of dozing or sleeping); higher scores indicate more daytime somnolence. The cut score to identify high-level of daytime sleepiness is > 16, which was only exhibited by individuals with moderate to severe obstructive sleep apnea syndrome in the original validation study (Johns, 1991). No patients exceeded the cut-off for daytime somnolence.

Depression. The ALS-Depression-Inventory (ADI-12; Hammer, Häcker, Hautzinger, Meyer, & Kübler, 2008) was used to assess depressive symptoms. The ADI-12 is a 12-item self-report scale designed for people with ALS/MND aimed to minimize bias due to somatic symptoms that may overlap with the MND disease process. The ADI-12 was validated using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV. The cut score to identify any possible depressive disorder is ≥ 23 (Hammer et al., 2008).

Emotional lability. The Center for Neurologic Study Lability Scale (CNS-LS; Moore et al., 1997) is a 7-item scale used to assess pathological laughing and crying. The CNS-LS has been validated for patients with neurological conditions including ALS. The cut score to identify affective lability is ≥ 13 (Moore et al., 1997).

2.4.2 Brief cognitive screens.

ALS Cognitive Behavioral Screen (ALS-CBS; Wooley et al., 2010). The ALS-CBS is a brief screening instrument tailored to patients with MND, recommended for the characterization of cognitive impairment in ALS per the Strong and colleagues (2017) diagnostic criteria. The ALS-CBS includes a cognitive and a behavioral screen, only the cognitive screen was used for the purposes of the present study. The cognitive screen includes items to tap abilities including attention, concentration, mental tracking/ monitoring[1], and verbal fluency, which are weighted towards executive functioning. The ALS-CBS was developed to be independent of patients' physical disability level. The ALS-CBS also includes a verbal fluency item (i.e., letter F[1] or S) that may be completed through either writing or speaking. Summing all cognitive items creates a total score, lower scores reflect worse cognitive functioning. The test developers reported that the ALS-CBS (cut-score < 17) demonstrated 85% sensitivity and 71% specificity for identifying any level of cognitive dysfunction, defined via the consensus criteria for ALS-cognitive impairment, ALS-behavioral impairment, and ALS-FTD combined (Strong et al., 2009). The cut-score for identifying ALS-FTD is < 10 (Woolley et al., 2010).

[1] Methodological note, because there are some overlapping tasks (e.g., letters F and S fluency, number and letter alternation) among the tests (e.g., ALS-CBS, ECAS, MoCA,

Edinburgh Cognitive and Behavioral ALS Screen (ECAS; Abrahams et al., 2014). The ECAS is a brief screening instrument tailored to patients with MND, recommended for the characterization of cognitive impairment in ALS per the Strong and colleagues (2017) diagnostic criteria. The ECAS includes a cognitive and a behavioral screen, only the cognitive screen was used for the purposes of the present study. The cognitive screen includes items to tap abilities including naming, verbal comprehension, spelling, verbal fluency, working memory[1], sentence completion, and social cognition, which together make up the ALS-Specific composite score. Additional items tap verbal memory and visuospatial abilities, which together make up the ALS Non-Specific composite score. The ECAS includes two verbal fluency items (i.e., words beginning with letter S[1] and four-letter words beginning with T) that may be completed through either writing or speaking and includes an adjustment for speed (i.e., *vfi* calculation; Abrahams et al., 2000). Lower scores reflect worse cognitive functioning. Cut scores are provided for the total ECAS score, ALS-Specific and ALS Non-Specific scores, and cognitive domain scores. The test developers reported that the ECAS total score (cut-score ≤ 105) demonstrated 77% sensitivity and 89% specificity, the ALS-Specific score (cut-score ≤ 77) demonstrated 69% sensitivity and 89% specificity, and the language domain score (cut-score ≤ 26) demonstrated 86% sensitivity and 64% specificity for identifying cognitive dysfunction, defined as performance ≤ 2 SDs on cognitive composites composed of a larger battery (Niven et al., 2015).

D-KEFS), each task was administered only once. Responses were transcribed to each test and scored as appropriate for each measure.

Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). The MoCA is a general cognitive screen that was designed as a rapid screening instrument for mild cognitive dysfunction. In the present study, the MoCA was used for the purposes of discriminant validity and comparison with tailored screening measures for MND. The MoCA includes items to tap abilities including visuospatial/executive abilities, naming, verbal memory, attention, repetition, verbal fluency, abstraction, and orientation. The MoCA includes three items that require motor abilities (i.e., visuospatial/executive drawing items), two items that require spoken repetition, and a verbal fluency item (i.e., letter F[1]). For patients that were unable to complete the motor items, the MoCA-BLIND was administered, which was developed for individuals who are visually impaired and omits visually presented items including the motor items (i.e., visuospatial/executive abilities and naming omitted; Wittich, Phillips, Nasreddine, & Chertkow, 2010). Summing all items creates a total score (MoCA standard max = 30; MoCA-BLIND max = 22), lower scores reflect worse cognitive functioning. The test developers reported that the standard MoCA (cut-score < 26) demonstrated 90% sensitivity and 87% specificity for identifying mild cognitive impairment and 100% sensitivity and 87% specificity for identifying mild Alzheimer's dementia (Nasreddine et al., 2005). The MoCA-BLIND (cut-score < 18) demonstrated 63% sensitivity and 98% specificity for identifying mild cognitive impairment and 94% sensitivity and 98% specificity for identifying mild Alzheimer's dementia (Wittich et al., 2010). Among patients with FTD behavioral-variant, a condition clinically related to MND, the standard MoCA (cut score < 17) demonstrated 78% sensitivity and 98% specificity (Freitas, Simões, Alves, Duro, & Santana, 2012). The present study will utilize the standard cut scores (i.e., Standard

MoCA < 26, MoCA-BLIND < 18) as well as a cut score specified for FTD behavioral-variant (i.e., Standard MoCA < 17).

2.4.3 Verbal fluency evaluation.

Verbal fluency. The Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Test (Delis, Kaplan, & Kramer, 2001) is a spoken verbal fluency test used in this study to primarily assess phonemic (letter) fluency. This paradigm involves several executive and expressive language abilities such as intrinsic word generation, word retrieval, verbal association, monitoring, and updating. Notably, verbal fluency tasks are also somewhat impacted by vocabulary size and lexical access speed during confrontation naming (Shao et al., 2014). The D-KEFS Verbal Fluency Test includes three conditions including phonemic letter fluency (i.e., FAS), semantic category fluency (i.e., animals and boys names), and a switching condition (i.e., alternating fruits and furniture); the latter is thought to more heavily assess an executive component. This test requires participants to orally produce as many words as possible that meet particular criteria (e.g., words beginning with letter F) within one minute. The *vfi* calculation was used to adjust for speaking speed, as recommended by the Strong and colleagues (2017) consensus criteria (*vfi* = 60 secs – secs to read words / correct words produced; Abrahams et al., 2000). Although, it is notable that there is lack of reliability information about the *vfi*. Healthy family members/caregivers served as controls ($N = 20$), patients' *vfi* scores were compared to the 5th percentile (Strong et al., 2017). The D-KEFS Verbal Fluency Test *vfi* was only administered to patients with adequate speech intelligibility, though some had dysarthria.

Patients with significant dysarthria but intact hand motor ability completed the Thurstone Word Fluency Test (Thurstone, 1938) an alternative written verbal fluency test. Participants were asked to write as many words as possible that meet particular criteria (e.g., words beginning with letter S within five minutes; four-letter words beginning with letter C within four minutes). In previous research, the Thurstone Word Fluency Test demonstrated adequate 6-week test-retest reliability in a mixed clinical sample (r = .79; Strauss et al., 2006). In the present sample, all but one patient who completed the Thurstone Word Fluency Test scored within normal limits using the standard scoring procedures (total administered n = 3). The one individual who scored within the impaired range had difficulty generating responses and provided no additional responses beyond three minutes into each task. Normative data for written *vfi* are also limited. Therefore, standard scoring procedures were retained for this task; combined raw scores were standardized by age, sex, race, and education, derived from a sample of N = 704 healthy adults (Heaton et al., 2004). Although verbal fluency is sometimes treated as a language domain measure, these tasks were considered separate from the *comprehensive language battery* per Strong and colleagues (2017), which classifies these impairments within the executive functioning domain. Phonemic fluency was the focus of the verbal fluency assessment per these criteria and the MND literature (Strong et al., 2017).

2.4.4 Comprehensive language battery.

Word production. The NAB Oral Production (Stern & White, 2003) subtest is a narrative picture description task used to assess expressive language, specifically speech/word production. Additional abilities are embedded within this task such as

naming and semantic knowledge. Patients are asked to verbally describe a picture of a family picnic and are given two minutes to respond. Responses are scored for their conveyance of the picture using a checklist of target content. One point is given for each target content-unit produced. NAB Oral Production was only administered to patients with adequate speech intelligibility, though some had dysarthria. For patients with significant dysarthria but intact hand motor ability, the NAB Writing (Stern & White, 2003) subtest was used as an alternative narrative picture description task to assess word production. Patients are asked to write a description of the same picture of a family picnic and given four minutes to respond. Responses are scored for conveyance of the picture content, spelling, and syntax. The NAB Oral Production and Writing subtests are similar to the BDAE-3 Cookie Theft picture task, though the former provides a more quantitative assessment approach and stronger standardization data (Stern & White, 2003). In order to assess for potential impact of verbal or written motor speed, patients' scores were recorded using the standard administration time (2 mins) as well as extra time during the same trial (extended to 2 mins and 30 seconds). However, all patients scored within normal limits for content conveyance within the standard administration time. In previous research, the NAB Oral Production subtest demonstrated high internal consistency ($\alpha \approx$ .80s), though ~6-month test-retest reliability was low in a healthy sample ($r < .60$; Strauss et al., 2006). Raw scores were standardized by age, sex, and education, derived from a sample of $N = 1{,}448$ healthy adults (Stern & White, 2003).

Confrontation naming. The NAB Naming (Stern & White, 2003) subtest is a 31-item color picture object-naming task used to assess expressive language through confrontation naming. Several abilities are embedded within this task such as perceptual

abilities, semantic knowledge, lexical access, and word retrieval (Migliaccio et al., 2016). NAB Naming is similar to the Boston Naming Test, though the former includes a larger standardization sample and may be less impacted by educational attainment (Harry & Crowe, 2014; Stern & White, 2003). In previous research, NAB Naming demonstrated adequate internal consistency ($\alpha \approx .70$s) and ~6-month test-retest reliability ($r \approx .70$s) in a healthy sample (Strauss et al., 2006). NAB Naming also demonstrated strong convergent validity with the Boston Naming Test validated in an aphasia sample ($r = .76$) and a TBI sample (*rs* .74 to .80; Harry & Crowe, 2014; Stern & White, 2003). Raw scores were standardized by age, sex, and education derived from a healthy sample (Stern & White, 2003).

Following commands. The MAE-3 Token Test (Benton et al., 1994) is a 22-item test used to assess receptive language through following commands. Several abilities are embedded within this task such as simple auditory comprehension, more complex syntax comprehension (e.g., order prepositions), basic semantic knowledge (i.e., colors, shapes), motor planning, short-term memory, and global cognitive functioning (Strauss et al., 2006). Patients are asked to follow increasingly complex commands using plastic tokens. Earlier items assess simple auditory comprehension (e.g., "point to a circle"); later items also assess syntax (e.g., "touch the green square *with* the black circle"). The MAE-3 Token Test is untimed but requires hand-motor functioning. Several patients with hand-motor weakness performed this task by using their stronger arm or grasping the tokens with two hands to compensate. Scoring is based on correctly following each command sequence, but not based on clumsiness or speed. Observed errors were often in the form of opposite sequencing and perseverative responses. Several comparable Token Test

versions exist, reliability is typically stronger in clinical samples; 10-month test-retest reliabilities were high in a dementia sample (*rs* .85 to .91, two versions) but low in healthy samples. Internal consistency evaluations suggest these tests assess two different language factors (i.e., simple and syntactically complex auditory comprehension) resulting in low alphas (Strauss et al., 2006). However, the Token Test demonstrates strong clinical utility for detecting various forms of aphasia, particularly receptive (Spreen & Risser, 2003; Strauss et al., 2006). MAE-3 raw scores were corrected for education and converted to standardized percentiles from a sample of $N = 350$ adults without evidence of neurologic disease (Benton et al., 1994).

For patients with hand weakness that were unable to manipulate the tokens but were able to point, the NAB Auditory Comprehension Colors/Shapes/Numbers subtest (Stern & White, 2003) was used as an alternative auditory commands task. Patients are asked to follow increasingly complex commands by pointing to images on a page in a certain order. This test was selected as an alternate task for its limited motor demands, though its psychometric properties were less desirable. In previous research, the NAB Auditory Comprehension composite score demonstrated low internal consistency ($\alpha <$ .60) and ~6-month test-retest reliability ($r <$ .60) in a healthy sample. These reliability results may reflect assessment of different language factors and ceiling effects in healthy samples, similar to the Token Test (Strauss et al., 2006). The NAB Auditory Comprehension Colors/Shapes/Numbers subtest was also validated in an aphasia sample and demonstrated moderate convergent validity with the MAE Token Test ($r = .55$; Stern & White, 2003). NAB raw scores were standardized by age, sex, and education derived from a healthy sample (Stern & White, 2003).

Repetition. The BDAE-3 Word Repetition (Goodglass et al., 2001) subtest is a 10-item test used to assess verbal repetition. Patients are asked to repeat single and multisyllable words. In previous research, the BDAE-3 Word Repetition subtest demonstrated high internal consistency in an aphasia sample ($\alpha = .88$; Goodglass et al., 2001), although there is lack of test-retest reliability information (Strauss et al., 2006). In the present study, this task was only administered to patients with adequate speech intelligibility, though some had dysarthria. Disentangling impaired repetition from motor-related dysarthria presents a challenge in this patient population. *Consistent* articulation difficulties were considered motor-related dysarthria, whereas repetition errors associated with aphasia are *variable* and may only appear under certain conditions (Goodglass et al., 2001). Repetition scoring was liberal within the present study, consistent articulation difficulties from dysarthria were not scored as repetition errors. In contrast, paraphasias were scored as repetition errors. In aphasia, two common types are phonemic and semantic paraphasias. Phonemic paraphasias are errors in which the sound structure produced is incorrect, often due to substituted, omitted, or transposed sounds. Semantic paraphasias are errors in which the word produced is incorrect but semantically related (Goodglass et al., 2001). One individual demonstrated a phonemic paraphasia during multisyllable repetition, without the presence of a consistent articulation difficulty (i.e., dysarthria).

Spelling. The MAE-3 Spelling Test (List C; Benton et al., 1994) is an 11-item test used to assess spelling. Patients are asked to spell auditory-presented words. Responses may be provided in written, spoken, or block letter formats, which is suitable for patients with MND. In previous research, alternate-form reliability indicated no significant

differences across versions, although there is lack of information about other forms of reliability (Strauss et al., 2006). Raw scores were corrected for education and converted to standardized percentiles derived from an adult sample without evidence of neurologic disease (Benton et al., 1994).

Reading comprehension. The BDAE-3 Sentences and Paragraphs (Goodglass et al., 2001) is a 10-item test used to assess reading comprehension, with difficulty ranging from first-grade through high-school level. Additional abilities are embedded within this task such as semantic knowledge, syntax comprehension, contextual inferences, and verbal reasoning. Patients are asked to read sentences and paragraphs and then provided four choices to complete the text. Responses may be provided in any format (e.g., spoken, written). Earlier items assess basic comprehension of sentences and single word response choices. Later items assess comprehension of paragraphs in which complex abilities are embedded. In previous research, the BDAE-3 Sentences and Paragraphs subtest demonstrated adequate internal consistency in an aphasia sample ($\alpha = .79$; Goodglass et al., 2001), although there is lack of test-retest reliability information (Strauss et al., 2006). BDAE-3 raw scores were converted to standardized percentiles from a disease sample of $N = 85$ patients with aphasia (Goodglass et al., 2001).

Syntax comprehension. The BDAE-3 Syntactic Processing (Goodglass et al., 2001) section includes three subtests (i.e., Touching A with B, Reversible Possessives, and Embedded Sentences) that assess receptive language through various aspects of syntax comprehension (e.g., order prepositions, possessive and passive subject-object relationships). Additional abilities are embedded within this task such as basic auditory comprehension and semantic knowledge. Patients are read sentences involving verbal

relationships and asked to select the picture that shows the relationship (e.g., "the child calling her mother has dark hair"). In previous research, the BDAE-3 Syntactic Processing subtests demonstrated adequate internal consistency in an aphasia sample (αs .71 to .79; Goodglass et al., 2001), although there is lack of test-retest reliability information (Strauss et al., 2006). Raw scores were converted to standardized percentiles derived from an aphasia sample (Goodglass et al., 2001).

Complex auditory comprehension. The BDAE-3 Complex ldeational Material (Goodglass et al., 2001) subtest is a two-part 12-item test used to assess receptive language through complex auditory comprehension. Several abilities are embedded within this task such as basic auditory comprehension, syntax comprehension (e.g., prepositions), verbal reasoning, contextual inferences, semantic knowledge, and short-term memory. During earlier items patients are asked yes or no questions based on simple knowledge, though syntax comprehension is embedded within the task (e.g. "do two pounds of flour weight more than one?"). During later items patients are asked yes or no questions in response to short stories read aloud. Responses may be provided in any format (e.g., spoken, written). In previous research, the BDAE-3 Complex ldeational Material subtest demonstrated high internal consistency in an aphasia sample (α = .80) and moderate correlation with the Syntactic Processing Embedded Sentences subtest (r = .68; Goodglass et al., 2001). Although there is lack of test-retest reliability information (Strauss et al., 2006). Raw scores were standardized by age, sex, and education, derived from a sample of N = 326 healthy adults (Heaton et al., 2004).

Verb processing. The Kissing and Dancing Test (KDT; Bak & Hodges, 2003) is a measure used to assess receptive language, verb processing, and semantic relationships.

Participants are presented with a target picture and asked to select between two picture response options. The correct response is a picture of a verb that is semantically related to the target stimulus (e.g., washing and ironing). Responses may be provided in any format (e.g., spoken, written, pointing). The KDT was selected for three primary reasons: (1) the KDT is recommended for the characterization of language impairment per the Strong and colleagues (2017) criteria, (2) unique assessment of verb processing, and (3) growing popularity within the MND/ALS, FTD, and aphasia literature. The KDT was developed and validated in a FTD sample. The authors suggest that poor performance reflect problems with verb processing, linked to frontal cortical regions (Bak & Hodges, 2003). However, there is lack of reliability information and standardization data are limited to a small healthy sample from the United Kingdom ($N = 20$; Bak & Hodges, 2003). The KDT was modeled after the Pyramids and Palm Trees Test, which demonstrated cultural influences suggesting culturally specific standardization data may be necessary (Klein & Buchanan, 2009). Healthy family members/caregivers served as culturally comparable controls ($N = 22$), patients' raw scores were compared to the 5th percentile (Strong et al., 2017).

2.5 Data Analyses

Raw cognitive test scores were converted to standardized scores based on standardization data to determine the relative standing of participants' test performance compared to either heathy controls or patients with aphasia. In most cases, standardization data was used from published literature. Local standardization data was collected from healthy controls for two measures (KDT and spoken *vfi*). Univariate analyses (e.g., means, standard deviations, frequencies, percentiles) were calculated in

Statistical Package for the Social Sciences (SPSS) version 25.

2.5.1 Gold standard impairment classification.

To address Aim 1 (Hypothesis 1), each test score from the comprehensive battery was classified as "impaired" or "not impaired" based on modified Strong et al. (2017) criteria (see the *Defining Impairment: Individual Test Level* for further details). Gold standard criteria were applied to classify language (or verbal fluency) impairments per Strong and colleagues (2017) MND/ALSci using impaired scores from the comprehensive language battery. Subgroups were constructed for descriptive purposes (see the *Defining Impairment: Diagnostic Level* for further details). Additionally, T-test and Chi square (χ^2) tests were used to evaluate potential demographic or clinical differences among those with language impairments and those with intact language functioning.

2.5.2 Cognitive screening operating characteristics.

To address Aim 2 (Hypotheses 2a and 2b), the three brief cognitive screens were evaluated for their relative operating characteristics. Published cut-scores were used to dichotomize scores into those suggestive of impairment (i.e., positive test sign) or intact functioning (i.e., negative test sign). The positive and negative test signs for each brief screen were compared with the gold standard language impairment classification criteria (MND/ALSci; Strong et al., 2017) using 2 x 2 contingency tables. Sample based point-estimates and 95% confidence intervals were calculated in Excel for the following operating characteristics: sensitivity, specificity, efficiency, positive predictive value (PPV), negative predictive value (NPV), and Cohen's kappa (Mackinnon, 2000; McKenzie, Vida, Mackinnon, Onghena, & Clarke, 1997).

Sensitivity is the proportion of people with the target condition, who have a positive test sign. In the present study, the sensitivity point-estimate this is the observed percentage of patients that met criteria for MND/ALSci in the language domain (Strong et al., 2017), who were correctly classified by the screen cut-score. Confidence intervals reflect estimates of the proportion of the MND population with language impairments that would be correctly classified by the screen cut-score (McKenzie et al., 1997).

Likewise, *specificity* is the proportion of people without the target condition, who have a negative test sign. In the present study, specificity is the proportion of patients with intact language functioning, who were correctly classified by the screen cut-score. *Efficiency* is the overall correct classification rate (true positives and true negatives). *PPV* is the conditional probability that an individual with a positive test sign has the target condition, determined by the prevalence of the condition. In the present study, PPV is the probability that a patient with an 'impaired' screen score has MND/ALSci in the language domain (Strong et al., 2017). Therefore, *NPV* is the conditional probability that a patient with a 'normal' screen score has intact language functioning. *Cohen's kappa* (κ) is a coefficient that summarizes level of agreement between two ratings when chance-level agreement is accounted for ($\kappa = 0$ indicates chance-level agreement and $\kappa = 1$ indicates complete agreement). In the present study, kappa compares agreement between the screen outcome ('impaired' or not) and the gold standard MND/ALSci language impairment classification. However, it is important to note that PPV, NPV, and kappa are all dependent on prevalence of the condition of interest, here MND/ALSci with language impairments. Poorer PPV and kappa values are common when prevalence is below 50% (Streiner, 2003).

In the context of the present study, the general focus is on *sensitivity* to language impairments. Specificity and NPV are less meaningful as the present gold standard criteria are focused on language (or verbal fluency) impairments exclusively. In other words, the gold standard for language dysfunction used in the present study does not assess for MND/ALSci in other cognitive domains (e.g., social cognition, executive functioning more broadly). Thus, "true negative" cases for overall MND/ALSci is unknown in this sample.

To address Aim 3, the cognitive screening measures were evaluated for their combined sensitivity. Various serial combinations of two screening indices were used to assess which combination produced the highest sensitivity. Screening results were combined using the 'believe the positive' approach, wherein the chained screening result was considered positive if the results of either screen was positive (Marshall, 1989; Thompson, 2003).

2.5.3 Cognitive screening interrelationships.

To address Hypothesis 2c, phi coefficients ($r\phi$) were calculated in SPSS to examine the magnitude of the relationships between the dichotomous outcomes (i.e., "impaired" or "not impaired") for the three brief cognitive screens (i.e., ALS-CBS, ECAS, and MoCA). $r\phi$ is similar to the Pearsons correlation coefficient but is intended for dichotomous variables. Chi square (χ^2) tests were used to test the significance of individual correlations. Convergent validity was assessed by correlating outcomes from the ALS-CBS with the ECAS ALS-Specific Score, both tailored for MND. Additionally, probability values were used to test whether two correlations significantly differ in magnitude. Discriminant validity was assessed by comparing the expected divergent

correlations (i.e., each tailored screen with the MoCA), to the expected convergent correlation (i.e., ALS-CBS with the ECAS ALS-Specific Score).

CHAPTER 3: RESULTS

3.1 Disease Characteristics

Table 4 presents patient disease characteristics. Most individuals had limb onset. Disease severity varied among the sample, though most were early enough in their illness that changes to speech or handwriting were only mild (ALSFRS-R speech and handwriting items modal rating = 3 for both). However, three patients were unable to speak and over half used assistive equipment for mobility. Approximately a third of the sample reported elevated emotional lability; the same proportion reported elevated depressive symptoms. None reported elevated levels of daytime somnolence.

Table 4. *Patient Disease Characteristics*	
Total MND *N*	41
Classic ALS *n*	35 (85.4%)
PLS *n*	5 (12.2%)
Familial MND	2 (4.8%)
Bulbar onset	5 (12.2%)
Limb onset	35 (85.4%)
Other onset [a]	1 (2.4%)
Disease Length and Severity	
Years since symptom onset *M* (*SD*)	4.44 (3.73)
Total ALSFRS-R *M* (*SD*)	30.10 (7.50)
Speech (ALSFRS-R item 1) *M* (*SD*)	2.98 (.96)
Handwriting (ALSFRS-R item 4) *M* (*SD*)	2.51 (1.17)
Assistive Devices	
Bipap use	12 (29.3%)
Continuous ventilation	0 (0%)
Feeding tube use	5 (12.2%)
Nonverbal communication	3 (7.3%)
Ambulates with walker/rollator	13 (31.7%)
Wheelchair mobility	11 (26.8%)
Self-Report Symptoms	
Emotion Lability (CNS-LS) *M* (*SD)*	11.02 (4.22)
elevated	12 (29.3%)
Depression (ADI-12) *M* (*SD*)	19.68 (4.75)
elevated	12 (29.3%)
Somnolence (ESS) *M* (*SD*)	4.76 (3.83)
elevated	0 (0%)

Note. Frequencies and percentages unless otherwise indicated. Total sample includes $n = 1$ adult with juvenile onset ALS, counted separately from the Classic ALS subgroup. ALSFRS-R = ALS Functional Rating Scale-Revised, total scores range from 0 (worst functional ability) to 48 (intact functional ability), items 1 and 4 range from 0 (unable) to 4 (normal); CNS-LS = Center for Neurologic Study Lability Scale, scores ≥ 13 suggest emotional lability; ADI-12 = ALS-Depression-Inventory, scores ≥ 23 suggest possible depressive disorder; ESS = Epworth Sleepiness Scale, scores > 16 suggest significant daytime somnolence; For the ALSFRS-R higher scores indicate better functional ability. For all other rating scales higher scores indicate worse symptoms. [a] Indicates that one individual reported simultaneous bulbar and limb onset.

3.2 Normative Data: Spoken *vfi* and KDT

Table 5 presents the local standardization data from healthy controls. Spoken *vfi* and KDT cut-scores scores indicate performance worse than or equal to the 5th percentile, used to identify patient impairments (Strong et al. 2017).

Table 5. *Local Standardization Data from Healthy Controls*

Measure	*N*	Mean (SD)	Skew	Kurtosis	5th %tile Cut-Scores
Kissing and Dancing Test raw score	22	50.59 (1.56)	-1.30	2.17	< 47
D-KEFS spoken *vfis*					
Letter F *vfi*	20	4.10 (1.43)	0.66	0.16	≥ 7.49
Letter A *vfi*	20	4.99 (2.01)	0.86	0.12	≥ 9.17
Letter S *vfi*	20	3.97 (1.47)	0.34	-0.49	≥ 6.96
Animals *vfi*	20	2.52 (0.69)	0.31	-0.16	≥ 4.04
Boys Names *vfi*	20	2.18 (0.46)	0.76	2.00	≥ 3.43
Fruits/Furniture Switching *vfi*	20	3.65 (0.83)	0.13	0.23	≥ 5.40

Note. Cut-scores indicate performance worse than or equal to the 5th percentile from healthy controls per Strong et al. (2017). D-KEFS = Delis-Kaplan Executive Function System; *vfi* = Verbal Fluency Index, which adjusts for speech speed (60 secs – secs to read words / correct words produced; Abrahams et al., 2000); *n* = 2 controls completed the Kissing and Dancing Test but did not complete the D-KEFS *vfi*; Higher *vfi* scores indicate worse verbal fluency; Lower Kissing and Dancing Test scores indicate worse verb processing.

3.3 Comprehensive Assessment: Task-Level Impairments

Descriptives of patients' performance on the verbal fluency tasks and comprehensive language battery are presented in Tables 6 and 7. It was hypothesized that the pattern of language dysfunction would resemble nonfluent/agrammatic aphasia (Gorno-Tempini et al., 2011), including prominent word production and syntax comprehension impairments (Aim 1, Hypothesis 1).

Overall, the most common impairments were on phonemic fluency tasks, classified within the executive domain (Strong et al., 2017). Altogether, the frequency of impairments on any phonemic fluency task was 34.1% (*n* = 14; impaired written fluency or ≥ 1 spoken *vfi* trial).

Table 6. *Patient Scores and Individual Impairments on the Spoken and Written Fluency Tasks*

Test	Ability/Function	Score	Norms	*N*	Mean (*SD*)	Cut-Score	Impaired *n* (%)
D-KEFS Spoken Verbal Fluency	Phonemic Fluency	F *vfi*	Local	38	5.69 (3.53)	≤ 5th %tile	10 (24.4%)
		A *vfi*	Local	38	6.67 (4.71)	≤ 5th %tile	6 (14.6%)
		S *vfi*	Local	38	5.29 (3.97)	≤ 5th %tile	7 (17.1%)
	Semantic Fluency	Animals *vfi*	Local	38	2.81 (1.34)	≤ 5th %tile	6 (14.6%)
		Boys Names *vfi*	Local	38	2.78 (0.90)	≤ 5th %tile	5 (12.2%)
	Switching Semantic Fluency	Switching Fruits/Furniture *vfi*	Local	37	4.14 (1.21)	≤ 5th %tile	6 (14.6%)
Thurstone Written Word Fluency Test	Phonemic & Restricted Fluency	Total T-score	Heaton	3	38 (13.75)	T ≤ 34	1 (2.4%)

Note. D-KEFS = Delis-Kaplan Executive Function System; *vfi* = Verbal Fluency Index, which adjusts for speech speed (60 secs – secs to read words / correct words produced; Abrahams et al., 2000). Sources for standardization data: Heaton norms (Heaton, Miller, Taylor, & Grant, 2004); Local norms (see Table 5).

Within the comprehensive language battery, the most common impairments were on syntax comprehension tasks. Altogether, the frequency of impairments on any of the three BDAE-3 Syntactic Processing tasks was 17.1% (*n* = 7) (Embedded Sentence*s* *n* = 4, 9.8%; Reversible Possessives *n* = 3, 7.3%; Touching A with B *n* = 2, 4.9%). The second most common language impairments were on confrontation naming and complex auditory comprehension (NAB Naming and BDAE-3 Complex ldeational Material each *n* = 4, 9.8%). Notably, confrontation naming generally improved with phonemic cueing, suggesting that poor performance was likely due to a word-retrieval impairment rather than a semantic storage impairment (Jefferies, Patterson, & Ralph, 2008). The next most common were impairments complex reading comprehension, verb processing (BDAE-3 Reading Comprehension Sentences & Paragraphs and KDT each *n* = 3, 4.9%), and following syntactically complex commands (MAE-3 Token Test *n* = 2, 4.9%). All comprehension errors were at the paragraph level, suggesting that difficulties were due to higher-order verbal abilities (BDAE-3 Complex ldeational Material and Reading Comprehension Sentences & Paragraphs). Impaired repetition and spelling were rare (BDAE-3 Word Repetition and MAE-3 Spelling Test each *n* = 1, 2.4%). One patient (2.4%) demonstrated impaired performance on the written picture description task due to spelling and syntax subscores, whereas conveyance of the scene was above average (NAB Writing). No patients were impaired on the verbal picture description task (NAB Oral Production) or written conveyance, which assess expressive language via word production.

Table 7. *Patient Scores and Individual Impairments on the Comprehensive Language Battery*

Ability/Function	Test	Norms	Cut-Score	*N*	Mean (*SD*)	Impaired *n* (%)
			Expressive Language			
Word Production	NAB Oral Production	NAB	≤ 5th %tile	38	76.66 %tile (19.54)	0 (0%)
	NAB Writing Total Score	NAB	≤ 5th %tile	3	49.00 %tile (41.57)	1[a] (2.4%)
Confrontation Naming	NAB Naming	NAB	≤ 5th %tile	41	53.76 %tile (28.20)	4 (9.8%)
			Repetition			
Repetition	BDAE-3 Word Repetition	BDAE-3	< 10 raw	39	9.97 raw (.16)	1 (2.4%)
			Receptive Language			
Syntax Comprehension	BDAE-3 Syntactic Processing Embedded Sentences	BDAE-3	≤ 50th %tile (aphasia)	41	89.02 %tile (17.15)	4 (9.8%)
	Reversible Possessives	BDAE-3	≤ 50th %tile (aphasia)	41	98.78 %tile (20.88)	3 (7.3%)
	Touching A with B	BDAE-3	≤ 50th %tile (aphasia)	41	90.00 %tile (17.46)	2 (5.3%)
Complex Auditory Comprehension	BDAE-3 Complex Ideational Material	Heaton	≤ 5th %tile	41	50.85 T-score (11.19)	4 (9.8%)
Following Commands	MAE-3 Token Test	MAE-3	≤ 5th %tile	35	56.63 %tile (27.58)	2 (4.9%)
	NAB Auditory Comprehension Colors/Shapes/Numbers	NAB	≤ 5th %tile	3	100 cumm% (.00)	0 (0%)
Verb Processing	KDT	Local	≤ 5th %tile	41	49.37 raw (2.53)	3 (7.3%)

Table 7. (Continued)

			Reading			
Reading Comprehension	BDAE-3 Sentences & Paragraphs	BDAE-3	≤ 50th %tile (aphasia)	40	87.75 %tile (21.30)	3 (7.3%)
			Spelling			
Spelling	MAE-3 Spelling Test	MAE-3	≤ 5th %tile	41	55.02 %tile (20.99)	1 (2.4%)

Note. BDAE-3= Boston Diagnostic Aphasia Examination Third Edition; KDT = Kissing and Dancing Test; MAE-3 = Multilingual Aphasia Examination Third Edition; NAB = Neuropsychological Assessment Battery; ≤ 5th %tile = percentile cut-score compared to a healthy standardization sample; ≤ 50th %tile (aphasia) = percentile cut-score compared to an aphasia standardization sample; cumm% = cumulative percent. Sources for standardization data: NAB norms (Stern & White, 2003); BDAE-3 aphasia norms (Goodglass, Kaplan, & Barresi, 2001); Heaton norms (Heaton, Miller, Taylor, & Grant, 2004); MAE-3 norms (Benton, Hamsher, & Sivan, 1994); Local norms (see Table 5). [a] One individual demonstrated impaired NAB Writing performance due to spelling and syntax but not conveyance of the picture scene.

It is possible that impaired scores are impacted by aging, educational attainment, or premorbid intelligence. Notably, confrontation naming scores were standardized based on age, sex, and education (Stern & White, 2003), though the verbal fluency and syntax comprehension tasks were standardized but not demographically corrected. Associations between patients' characteristics (i.e., age, education, and Barona estimated FSIQ) and the most common impairments (i.e., verbal fluency, confrontation naming, and syntax comprehension) were considered. Pearsons correlations revealed that age, education, and estimated FSIQ were not significantly associated with the phonemic *vfi*s, NAB Naming, or the BDAE-3 Syntactic Comprehension tasks (*rs* .01 to .30, all *ps* > .05).

Regarding Hypothesis 1, overall language dysfunction observed in this MND sample did not particularly resemble a nonfluent/agrammatic pattern. However, a portion of the hypothesis was supported, difficulties with syntax comprehension were prominent. The most common language impairments were on tasks that directly assess syntax comprehension. Impairments on additional complex comprehension tasks with embedded syntax were also common (e.g., BDAE-3 Sentences & Paragraphs, Complex Ideational Material, and MAE-3 Token Test). Contrary to the hypothesis, there was not evidence of consistent expressive language/nonfluent impairments. No patients exhibited impairments in word production/conveyance on the picture description tasks. Rather, difficulties with confrontation naming were prominent.

3.4 Comprehensive Language Assessment: Diagnostic Evaluation

Table 8 presents subgroups that met diagnostic criteria for MND/ALSci (Strong et al., 2017) with impairments in the verbal fluency and/or language domains. Three subgroups were constructed: (1) MND/ALSci-L classified by ≥ 2 impaired tasks from the

comprehensive language battery (excluding verbal fluency; all had ALS), (2) MND/ALSci-VF classified by impaired written fluency or ≥ 2 phonemic *vfi* trials, and (3) MND/ALSci-L+VF classified by ≥ 2 impaired language tasks and impaired verbal fluency (all had ALS).

Table 8. *MND/ALSci Language and Verbal Fluency Diagnostic Classification Subgroups*

Subgroup	Criteria	MND type *n* ALS/PLS	Onset *n* Limb/Bulbar	Handed *n* Right/Left	Total *n* (%)
ALSci-L	≥ 2 language tasks impaired without evidence of ALSci-VF	4 / 0	4 / 0	4 / 0	4 (9.8%)
MNDci-VF	Impaired written fluency or ≥ 2 phonemic *vfi* trials, without evidence of MNDci-L	3 / 2	5 / 0	3 / 2	5 (12.2%)
ALSci-L+VF	≥ 2 language tasks *and* impaired verbal fluency	4 / 0	3 / 1	4 / 0	4 (9.8%)
Intact Verbal Fluency and Language	Above criteria not met	24 / 3	23 / 4 [a]	23 / 5	28 (68.2%)

Note. ALSci-L = ALS with cognitive impairment in the language domain; MNDci-VF = ALS or PLS with verbal fluency impairment; ALSci-L+VF = ALS with language and verbal fluency impairment. [a] Indicates that one individual reported simultaneous bulbar and limb onset.

Table 9 presents impairments and deficits by diagnostic subgroup to illustrate language dysfunction patterns. Although frank impairments (≤ 5th percentile) are the basis of the MND/ALSci classifications (Strong et al., 2017), several patients within the three subgroups also demonstrated borderline performance. These scores that may reflect indicate decline from premorbid cognitive functioning (6th and 9th percentiles per Benton et al., 1994; 'mildly impaired' T = 39-35 per Brooks et al., 2011). Therefore, borderline deficits are included in Table 9 for descriptive purposes. However, these observations should be interpreted with caution.

The ALSci-L subgroup (n = 4) had an average of 2.5 impaired scores from the comprehensive language battery. The ALSci-L subgroup had fairly consistent performance that appeared to be primarily characterized by poor syntax comprehension. All patients with ALSci-L demonstrated impaired performance on tasks that directly assess syntax comprehension or complex comprehension tasks that place demands on syntax comprehension (i.e., BDAE-3 Complex ldeational Material, Paragraph Reading Comprehension, or MAE-3 Token Test). Most also demonstrated poor performance (impairments or borderline deficits) on confrontation naming and/or verb processing (each n = 3). Although no patients assigned to the ALSci-L subgroup met criteria for verbal fluency impairment (≥ 2 phonemic *vfi* trials impaired), half had borderline performance (i.e., 1 phonemic *vfi* trial, n = 2). Word production, spelling, and repetition were intact in this subgroup.

The ALSci-L+VF subgroup (n = 4) had an average of 3.25 impaired scores from the comprehensive language battery (excluding verbal fluency). Performance reflected

mixed language impairments in this subgroup, though phonemic fluency was consistently affected. More specifically, half exhibited poor performance (impairments or deficits) on *both* confrontation naming and comprehension tasks involving syntax ($n = 2$). One patient had impaired confrontation naming, though syntax comprehension appeared intact. In contrast, another patient had impaired syntax comprehension, though naming appeared intact. Furthermore, half of the ALSci-L+VF subgroup demonstrated impaired verb processing ($n = 2$), whereas the other half did not. The most severely affected patient in this subgroup also demonstrated impaired repetition and spelling. Word production and reading comprehension were intact in this subgroup.

Finally, all patients in the MNDci-VF subgroup ($n = 5$) had phonemic fluency impairments. Although no patients with MNDci-VF met criteria for broader language dysfunction (≥ 2 impaired language tasks), one patient had impaired performance on one complex comprehension task. Another patient had borderline performance on two complex comprehension tasks. Yet another patient had borderline spelling performance.

Table 9. *Impairments and Borderline Deficits by MND/ALSci Subgroup*

Ability/Function	Deficit Level	ALSci-L+VF (*n* = 4)	ALSci-L (*n* = 4)	MNDci-VF (*n* = 5)	Intact (*n* = 28)
		Expressive Language			
Combined Phonemic Fluency (Spoken or Written)	*Impaired* (written impaired or ≥ 2 phonemic *vfi* trials)	4 (100%)	0 (0%)	5 (100%)	0 (0%)
	Borderline (1 phonemic *vfi* trial)	--	2 (50%)	--	3 (10.7%)
Confrontation Naming	*Impaired* (≤ 5th %tile)	2 (50%)	2 (50%)	0 (0%)	0 (0%)
	Borderline (6-15th %tile)	1 (25%)	1 (25%)	0 (0%)	3 (10.7%)
Word Production/ Content Conveyance	*Impaired* (≤ 5th %tile)	0 [a] (0%)	0 (0%)	0 (0%)	0 (0%)
	Borderline (6-15th %tile)	0 [a] (0%)	0 (0%)	0 (0%)	0 (0%)
		Repetition			
Repetition	*Impaired* (raw < 10)	1 (25%)	0 (0%)	0 (0%)	0 (0%)
		Receptive Language			
Syntactic Comprehension	*Impaired* (≥ 1 BDAE-3 Syntax subtest)	3 (75%)	1 (25%)	0 (0%)	3 (10.7%)
Following Commands	*Impaired* (≤ 5th %tile)	1 (25%)	1 (25%)	0 (0%)	0 (0%)
	Borderline (9th %tile)	0 (0%)	0 (0%)	1 (20%)	0 (0%)
Complex Auditory Comprehension	*Impaired* (T ≤ 34)	1 (25%)	2 (50%)	1 (20%)	0 (0%)
	Borderline (T = 39-35)	0 (0%)	1 (25%)	1 (20%)	1 (3.6%)
Verb Processing	*Impaired* (raw < 47)	2 (50%)	1 (25%)	0 (0%)	0 (0%)
	Borderline (raw < 48)	0 (0%)	2 (50%)	0 (0%)	1 (3.6%)
		Reading			
Paragraph Reading Comprehension	*Impaired*	0 (0%)	2 (50%)	0 (0%)	1 (3.6%)
		Spelling			
Spelling	*Impaired* (< 6th %tile)	1 (25%)	0 (0%)	0 (0%)	0 (0%)
	Borderline (6th %tile)	0 (0%)	0 (0%)	0 (0%)	2 (7.1%)

Note. Frequencies and percentages; ALSci-L = ALS with cognitive impairment in the language domain; MNDci-VF = ALS or PLS with verbal fluency impairment; ALSci-L+VF = ALS with language and verbal fluency impairments. BDAE-3= Boston Diagnostic Aphasia Examination Third Edition; *vfi* = Verbal Fluency Index, which adjusts for speech speed (60 secs – secs to read words / correct words produced; Abrahams et al., 2000). [a] One individual demonstrated impaired NAB Writing performance due to spelling and syntax but not conveyance of the scene content, therefore their performance is not reported as impaired here.

3.4.1 Characteristics by Language Impairment Status

Potential differences in demographics and disease characteristics between patients that met criteria for language impairments (ALSci-L and ALSci-L+VF subgroups combined) and those with intact language functioning were examined. The impaired language group (n = 8) was compared to all patients with MND and intact language functioning (n = 33) and those with ALS and intact language functioning (n = 27; see Table 10).

No group differences were observed (all ps > .05), including no significant differences in age, education, or Barona estimated FSIQ for those that met criteria for language impairments and all patients with MND that did not (ts -.720 to .630, all ps > .05). Additionally, there were also no significant differences in age, education, or estimated FSIQ for those that met criteria for language or verbal fluency impairments (i.e., ALSci-L, ALSci-L+VF, and MNDci-VF; all impaired subgroups combined) and those that did not (ts -.104 to .708, all ps > .05).

Table 10. *Patient Demographics and Disease Characteristics by Language Impairment Status*

	Language Impaired	Language Intact Total	Language Intact ALS only
N	8	33	27
Age *M* (*SD*)	57.75 (14.94)	61.76 (10.08)	60.78 (10.26)
Education yrs. *M* (*SD*)	14.38 (2.62)	14.21 (2.46)	13.96 (2.38)
Estimated FSIQ *M* (*SD*)	110.32 (6.37)	108.68 (7.42)	108.01 (7.27)
Right handed	8 (100%)	26 (78.8%)	21 (77.8%)
Male	6 (75%)	20 (60.6%)	18 (66.7%)
Disease Characteristics			
Familial MND	0 (0%)	2 (6.1%)	2 (7.4%)
Bulbar onset[a]	1 (12.5%)	4 (12.1%)	3 (11.1%)
Yrs. since symptom onset	4.44 (3.25)	4.44 (3.88)	3.62 (2.86)
Total ALSFRS-R *M* (*SD*)	29.00 (5.16)	30.36 (8.01)	29.67 (8.27)
Speech item 1 *M* (*SD*)	2.63 (1.89)	3.06 (.90)	3.15 (.86))
Handwriting item 4 *M* (*SD*)	2.38 (.74)	2.55 (1.25)	2.44 (1.37)
Assistive Devices			
Bipap use	4 (50%)	8 (24.2%)	8 (29.6%)
Feeding tube use	1 (12.5%)	4 (12.1%)	4 (14.8%)
Self-Report Symptoms			
CNS-LS *M* (*SD)*	12.25 (4.13)	10.73 (4.25)	10.96 (4.30)
ADI-12 *M* (*SD*)	19.00 (3.74)	19.85 (5.00)	20.26 (5.20)
ESS *M* (*SD*)	4.50 (4.18)	4.82 (3.80)	4.63 (3.35)

Note. Frequencies and percentages unless otherwise indicated. Language Impaired = subsample with cognitive impairment in the language domain per Strong et al., 2017 (ALSci-L and ALSci-L+VF combined); Language Intact Total = total MND sample with intact language functioning; Language Intact ALS only = subsample with classic ALS and intact language functioning (other disease types not included to aid comparisons); ALSFRS-R = ALS Functional Rating Scale-Revised; CNS-LS = Center for Neurologic Study Lability Scale; ADI-12 = ALS-Depression-Inventory; ESS = Epworth Sleepiness Scale, scores; For the ALSFRS-R higher scores indicate better functional ability. For all other rating scales higher scores indicate worse symptoms. [a] Indicates that one individual reported simultaneous bulbar and limb onset was counted in this group; *Indicates significant group difference (T-test or Chi-Square) between Language Impaired and Intact subgroups ($p < .05$; none observed).

3.5 Cognitive Screening

For the cognitive screening portion of the study, two screens tailored to MND (ALS-CBS and ECAS) and one general screen (MoCA) were evaluated. Table 11 presents descriptives and outcome classifications for each screen. In total, the ALS-CBS

Total score classified 73.2% of the sample (n = 30) as having some level of cognitive impairment. Three patients' scores (7.3%) fell below the alternative cut-score used to identify potential FTD.

Similarly, altogether the ECAS classified 75.6% of the sample (n = 31) of as having a cognitive impairment on any one or more scores. Agreement between the ALS-CBS Total score and ECAS (≥1 impairment) was 87.8% (both impaired: 68.3%, n = 28; both not impaired: 19.5%, n = 8), though agreement was lower (75.6%) with the ECAS ALS-Specific Score (both impaired: 48.8%, n = 20; both not impaired: 26.8%, n = 11).

Regarding the ECAS disease specific subscores, 48.8% (n = 20) were impaired on the ALS-Specific Score, 43.9% (n = 18) on the verbal fluency portion, 39.0% (n = 16) on the executive functioning portion, and 34.1% (n = 14) on the language portion. For the ECAS Non-Specific Score, 17.1% (n = 7) were impaired, 24.4% (n = 10) on the memory portion and 4.9% (n = 2) on the visuospatial portion.

Thirty-nine patients (95.1%) were able to complete the MoCA, 28 completed the standard version and 11 completed the MoCA-BLIND due to hand-motor weakness. Altogether, the MoCA classified 35.9% of the subsample (n = 14; 34.1% of the total sample) as having a cognitive impairment on either version using the standard cut-scores. No patients scored below the alternative cut-score used to identify potential FTD (Freitas et al., 2012).

Table 11. *Brief Cognitive Screening Scores and Outcome Classifications*

Screen	Score	*N*	Mean (*SD*)	Cut-Score	Classified Impaired *n* (%)
ECAS	Total (136 max)	41	104.05 (13.65)	≤ 105	18 (43.9%)
	Language (28 max)	41	26.17 (2.26)	≤ 26	14 (34.1%)
	Verbal Fluency (24 max)	41	14.98 (5.82)	≤ 14	18 (43.9%)
	Executive (28 max)	41	35.76 (5.10)	≤ 33	16 (39.0%)
	ALS-Specific Score (100 max)	41	76.88 (10.53)	≤ 77	20 (48.8%)
	Memory (24 max)	41	15.46 (4.76)	≤ 13	10 (24.4%)
	Visuospatial (12 max)	41	11.71 (0.64)	≤ 10	2 (4.9%)
	ALS-Nonspecific Score (36 max)	41	27.17 (5.05)	≤ 24	7 (17.1%)
	Number of impaired scores (8 max)	41	2.59 (2.43)	≥ 1	31 (75.6%)
ALS-CBS	Total (20 max)	41	14.88 (3.00)	< 17	30 (73.2%)
				< 10 [a]	3 (7.3%)
MoCA	Total (30 max)	28	25.68 (3.38)	< 26	9 (22.0%)
				< 17 [a]	0 (0%)
MoCA-BLIND*	Total (22 max)	11	17.82 (2.32)	< 18	5 (12.2%)
MoCA Combined	--	39	--	< 26/18	14 (34.1%)

Note. ALS-CBS = ALS Cognitive Behavioral Screen Cognitive Score; ECAS = Edinburgh Cognitive and Behavioral ALS Screen Cognitive Score; MoCA = Montreal Cognitive Assessment Standard Form 7.1; MoCA-BLIND = adapted version developed for individuals who are visually impaired and omits visually presented items including the motor items (visuospatial/executive abilities and naming omitted; Wittich et al., 2010); Combined MoCA = outcomes for both the standard and MoCA-BLIND versions.
*Although the MoCA-BLIND omits the naming items, patients were administered these items and all patients performed perfectly, though no points were given for the naming items.
[a] Indicates alternate cut-scores that identify potential FTD.

3.5.1 Cognitive screening: Detection of language impairments.

To address Aim 2 (Hypotheses 2a and 2b), operating characteristics were calculated for each cognitive screen based on comparisons to the gold standard language impairment criteria (i.e., MND/ALSci in the language domain, including both ALSci-L+VF and ALSci-L subgroups; Strong et al., 2017). Table 12 presents the cognitive screening operating characteristics for detecting all patients that met criteria for language impairments. Notably, the ECAS Language subscore is the primary measure of interest, which is the only index that targets language functioning exclusively. Because the present assessment focused on depth within the language domain, breadth across other cognitive domains was sacrificed due to feasibility and tolerability for this patient population. Thus, specificity values and overall classification indices are less meaningful for indices beyond the ECAS Language subscore as the present assessment focused on language impairments. However, sensitivity values are of particular interest across all measures.

Contrary to the hypothesis, the ECAS Language subscore and standard cut-score (≤ 26) provided low sensitivity (50%), at the point-estimate, and modest specificity (70%) for detecting language impairments in this sample (ALSci-L+VF and ALSci-L combined). However, 95% confidence intervals were wide. Potential sensitivities ranged from very low (16%) at the lower bound, to moderate (84%) at the upper bound. Likewise, potential specificities ranged from low (51%) to moderate (84%) at the lower and upper bounds respectively. Overall classification accuracy was 66% and not significantly better than chance level classification accuracy ($\kappa = .15$, 95% CI [-.15, .45], $p = .29$). Use of demographically adjusted cut-scores for the ECAS Language subscore also resulted in low sensitivity (50%) to language impairments, though specificity

improved (85%; Pinto-Grau et al., 2017). Overall classification accuracy increased to 78%, which was significantly better than chance (κ = .33, 95% CI [-.01, .68], p = .03). The predictive value of a negative test sign (NPV 88%) was much stronger than the predictive value of a positive test sign (PPV 44%).

Unexpectedly, the ECAS Verbal Fluency and Executive subscores were more sensitive to language impairments (63% each) than the ECAS Language subscore. Among the ECAS subscores, the ALS-Specific composite score had the highest sensitivity (75%) to language impairments, although modest. The ALS-CBS sensitivity to language impairments was 100%. The MoCA (standard and MoCA-BLIND versions combined), a general screening measure, exhibited better sensitivity (71%) to language impairments than the ECAS Language subscore, but modest.

In sum, Hypothesis 2a was partially supported. This hypothesis predicted higher sensitivity to language impairments for both the tailored MND screens (ALS-CBS and ECAS) compared to the MoCA. Results revealed that sensitivity to language impairments in MND was much higher for the ALS-CBS than the MoCA, but similar for both the ECAS ALS-Specific composite score and MoCA in this sample. The MoCA also demonstrated better sensitivity to language impairments than the ECAS Language subscore. Furthermore, Hypothesis 2b was not supported. This hypothesis predicted that the ECAS would demonstrate the highest sensitivity to language impairments in MND, compared to the ALS-CBS and MoCA. One concern was that the ALS-CBS and MoCA may leave more patients with language impairments undetected due to potentially limited assessment scope, yet this was not the case. Results revealed that the ALS-CBS detected all individuals with language impairments in this sample, though this result should be

considered in light of the high rate of positive test signs observed for this screen (73.2%, see Table 11). Sensitivities from the ECAS ALS-Specific score and the MoCA were modest, and sensitivity from the ECAS Language subscore was low.

Table 12. *Brief Cognitive Screening Operating Characteristics for Detecting Total with Language Impairments (ALSci-L+VF and ALSci-L combined)*

	ECAS Language	ECAS Verbal Fluency	ECAS Executive	ECAS ALS-Specific	ALS-CBS Total	MoCA/ MoCA-BLIND
N	41	41	41	41	41	39 (28/11)
Cut-score	≤ 26	≤ 14	≤ 33	≤ 77	< 17	< 26/17
Sensitivity	.50	.63	.63	.75	1.00	.71
95% CI	[.16 - .84]	[.24 - .91]	[.24 - .91]	[.35 - .97]	[.63 - 1.00]	[.29 - .96]
Specificity	.70	.61	.67	.58	.33	.72
95% CI	[.51 - .84]	[.42 - .77]	[.48 - .82]	[.39 - .75]	[.18 - .52]	[.53 - .86]
Efficiency	.66	.61	.66	.61	.46	.72
95% CI	[.49 - .80]	[.45 - .76]	[.49 - .80]	[.45 - .76]	[.31 - .63]	[.55 - .85]
Kappa	.15	.16	.21	.21	.16	.31*
95% CI	[-.15 - .45]	[-.11 - .42]	[-.07 - .49]	[-.03 - .45]	[.03 - .29]	[.02 - .61]
PPV	.29	.28	.31	.30	.27	.36
95% CI	[.08 - .58]	[.10 - .53]	[.11 - .59]	[.12 - .54]	[.12 - .46]	[.13 - .65]
NPV	.85	.87	.88	.90	1.00	.92
95% CI	[.66 - .96]	[.66 - .97]	[.69 - .97]	[.70 - .99]	[.72 - 1.00]	[.74 - .99]

Note. Point-estimates and 95% confidence intervals (Mackinnon, 2000; McKenzie et al., 1997). Gold Standard: Total with Language Impairment $n = 8$ (19.5%); ALSci-L = ALS with cognitive impairment in the language domain; ALSci-L+VF = ALS with language and verbal fluency impairments; ALS-CBS = ALS Cognitive Behavioral Screen Cognitive Score; ECAS = Edinburgh Cognitive and Behavioral ALS Screen Cognitive Score; MoCA = Montreal Cognitive Assessment Standard Form 7.1; MoCA-BLIND = adapted version developed for individuals who are visually impaired and omits visually presented items including the motor items (visuospatial/executive abilities and naming omitted; Wittich et al., 2010). *$p < .05$; **$p < .01$, significant kappa values indicate that screening agreement with the gold standard criteria was significantly better than chance-level.

3.5.2 Cognitive screening: Serial combinations.

To address Aim 3, serial combinations assessed whether chaining two screens produced the higher sensitivity. The 'believe the positive' approach was used (i.e., either screen is positive; Marshall, 1989; Thompson, 2003). The ALS-CBS exhibited 100% sensitivity to language impairments and was therefore not included in these combined

analyses. Table 13 presents the cognitive screening operating characteristics for detecting all patients that met criteria for MND/ALSci within the language domain specifically (i.e., ALSci-L+VF or ALSci-L). Chaining the ECAS Language subscore with the ECAS Verbal Fluency subscore did not increase sensitivity above the ECAS ALS-Specific composite score alone (75% sensitivity, see Table 12). Chaining the ECAS ALS-Specific composite score with the MoCA (standard or MoCA-BLIND version) resulted in higher sensitivity (88%), but also increases administration time for those that complete both screens (approx. 25 to 30 mins combined). Likewise, applying the 'believe the negative' approach (i.e., either screen was negative) to chaining the ECAS Language subscore with the ECAS Verbal Fluency subscore resulted in higher specificity (82%) but very low sensitivity (25%).

Table 13. *Chained Screening Operating Characteristics for Detecting Total with Language Impairments (ALSci-L+VF and ALSci-L combined)*

	Combined ECAS Language + ECAS Verbal Fluency	Combined ECAS ALS-Specific + MoCA/MoCA-BLIND
N	41	41
Cut-scores	ECAS Language ≤ 26 Verbal Fluency ≤ 14	ECAS ≤ 77 MoCA < 26/17
Sensitivity	.75	.88
95% CI	[.35 - .97]	[.47 – 1.00]
Specificity	.45	.45
95% CI	[.28 - .64]	[.28 - .64]
Efficiency	.51	.54
95% CI	[.35 - .67]	[.37 - .69]
Kappa	.12	.18
95% CI	[-.09 - .32]	[-.01 - .37]
PPV	.25	.28
95% CI	[.10 - .47]	[.12 - .49]
NPV	.88	.94
95% CI	[.64 - .99]	[.70 - 1.00]

Note. Believe the positive approach applied to chained screening results. Point-estimates and 95% confidence intervals (Mackinnon, 2000; McKenzie et al., 1997). Gold Standard: Total with Language Impairments *n* = 8 (19.5%); ALSci-L = ALS with cognitive impairment in the language domain; ALSci-L+VF = ALS with language and verbal fluency impairments; ECAS = Edinburgh Cognitive and Behavioral ALS Screen Cognitive Score; MoCA = Montreal Cognitive Assessment Standard Form 7.1; MoCA-BLIND = adapted version developed for individuals who are visually impaired, omits motor items. **p* < .05; ***p* < .01, significant kappa values indicate that screening agreement with the gold standard criteria was significantly better than chance-level.

3.5.3 Cognitive screening: Convergent and discriminant validity.

Hypothesis 2c addressed convergent and discriminant validity of the three brief cognitive screens (i.e., ALS-CBS, ECAS, and MoCA). Table 14 presents phi coefficients among the dichotomous outcomes (i.e., 'impaired' or not) from each screening score. It was expected that tailored MND cognitive screens would assess a common construct (i.e., the MND cognitive profile). Significantly higher correlations were hypothesized for convergent screening measures (i.e., the ALS-CBS Total Score correlated with the ECAS

ALS-Specific Score) and lower correlations for divergent measures (i.e., the ALS-CBS and ECAS correlated with the MoCA).

As hypothesized, outcomes on the ALS-CBS and the ECAS ALS-Specific composite score were strongly correlated [$r\phi = .59$; $\chi^2(1, N = 41) = 14.32$, $p < .001$], suggestive of convergent validity. Additionally, correlations between the ALS-CBS and the ECAS ALS-Specific subscores were moderate (i.e., Language, Verbal Fluency, and Executive $r\phi$*'s* = .32 - .43), whereas correlations with the ECAS ALS-Nonspecific scores were weak and not significant (i.e., Memory and Visuospatial; $r\phi$*'s* = .12 - .28).

There were weak and non-significant correlations between outcomes on the MoCA (standard version and MoCA-BLIND combined) and each of the tailored MND screening measures [ALS-CBS Total $r\phi = .11$; $\chi^2(1, N = 39) = 0.50$, $p = .48$; ECAS ALS-Specific Score $r\phi = .27$; $\chi^2(1, N = 39) = 2.89$, $p = .09$]. The expected divergent correlation between the ALS-CBS and the MoCA ($r\phi = .11$) was significantly different ($p = .015$) from the expected convergent correlation (ALS-CBS and the ECAS ALS-Specific composite score; $r\phi = .59$), suggestive of discriminant validity for the ALS-CBS.

In contrast, the expected divergent correlation between the ECAS ALS-Specific composite score and the MoCA ($r\phi = .27$) was not significantly different ($p = .08$) from the convergent correlation ($r\phi = .59$). Therefore, contrary to the hypothesis, discriminant validity was not demonstrated for the ECAS ALS-Specific composite score. Furthermore, outcomes on the MoCA were moderately correlated with outcomes on the ECAS Total Score and some of the ALS-Specific subscores (i.e., Language and Verbal Fluency; $r\phi$*'s* = .34 - .46), suggesting some overlap in these screening assessments. Although, outcomes

on the MoCA were not significantly correlated with outcomes on the ECAS Executive subscore [$r\phi = .29$; $\chi^2(1, N = 39) = 3.22$, $p = .07$].

Table 14. *Phi Coefficients Among Dichotomous Outcomes from Convergent and Divergent Cognitive Screens*

	ALS-CBS Outcome ($n = 41$)	Combined MoCA Outcome ($n = 39$)
ALS-CBS Outcome	--	.11 [d]†
ECAS Language Outcome	.32*	.44**
ECAS Verbal Fluency Outcome	.43**	.46**
ECAS Executive Outcome	.37*	.29
ECAS ALS-Specific Outcome	.59** [c]	.27 [d]
ECAS Memory Outcome	.22	.50**
ECAS Visuospatial Outcome	.12	.07
ECAS ALS-Nonspecific Outcome	.28	.57**
ECAS Total Score Outcome	.54**	.34*

Note. [c] Indicates hypothesized convergent relationship; [d] Indicates hypothesized divergent relationships; ALS-CBS = ALS Cognitive Behavioral Screen Cognitive Score; ECAS = Edinburgh Cognitive and Behavioral ALS Screen Cognitive Score; Combined MoCA = outcomes for either the Montreal Cognitive Assessment Standard Form 7.1 or adapted MoCA-BLIND version that omits motor items. *indicates correlation $p < .05$, ** indicates correlation $p < .01$. † indicates significant difference ($p < .05$) from the convergent correlation between the ALS-CBS and ECAS ALS-Specific composite score ($r\phi = .59$).

CHAPTER 4: DISCUSSION

The present study addressed the cognitive profile of MND and brief cognitive screening, with a focus on language impairments. Two primary aims were examined. First, characterization of language dysfunction in MND. Second, empirical evaluation of three brief cognitive screens, the ALS-CBS, ECAS, and MoCA.

4.1 MND Cognitive Profile: Language Dysfunction

Previous research suggests that a "predominantly linguistic" cognitive phenotype may exist in MND, which some posit may be more common that executive dysfunction (Taylor et al., 2013). The present study used a comprehensive and objective language battery to systematically assess for language dysfunction in MND, guided by progressive aphasia syndromes (Gorno-Tempini et al., 2011). Attention was paid to both intact and compromised language abilities to identify patterns and inform future research (Strong et al., 1996). Although previous language assessments in MND/ALS exist, to my knowledge the present study is the first to systematically examine the broad range of abilities suggested for comprehensive evaluation, that is: reading, spelling, repetition, speech production, verbal comprehension, semantic knowledge, and confrontation naming (Gorno-Tempini et al., 2011; Lezak et al., 2012). The present results support the existence of language dysfunction in the MND cognitive profile. However, MND/ALSci within the language domain affected a modest proportion of the present MND sample (19.5% total MND sample; 23.5% right-handed ALS subsample). This rate is somewhat lower than a previous report from a right-handed ALS sample without dementia (39%; Taylor et al., 2013), but similar to disordered language reported from an unselected MND cohort (28%; Rakowicz & Hodges, 1998).

4.1.1 Language characteristics.

Given the nature of MND, it was expected that language dysfunction in this population would resemble impairments similar to nonfluent/agrammatic progressive aphasia, which predominantly affects left posterior fronto-insular brain regions (Gorno-Tempini et al., 2011). Nonfluent/agrammatic progressive aphasia is characterized by "labored speech, agrammatism in production, and/or comprehension, variable degrees of anomia, and phonemic paraphasias, in the presence of relatively preserved word comprehension" (Gorno-Tempini et al., 2004, p. 2). Thus, it was expected that language dysfunction in MND would affect two characteristics in particular: (1) a prominent nonfluent characteristic, albeit milder than frank aphasia, along with (2) prominent syntax difficulties (Gorno-Tempini et al., 2011). It was postulated that these characteristics may arise from selective neuronal vulnerability potentially spreading from the motor cortex into pre-motor areas.

The first expected impairment, nonfluency, is sometimes used to describe patterns of reduced speech in aphasias. *Nonfluency/Fluency characteristics* refer broadly to speech output and flow including aspects such as phrase length, substantive content, and grammatical complexity (Goodglass et al., 2001). There are two important distinctions regarding this terminology. *Fluency characteristics* of language dysfunction are not to be confused with *verbal fluency tasks* (i.e., phonemic letter and semantic category fluency), which can be impaired for a variety of reasons (Shao et al., 2014). In other words, phonemic or semantic fluency tasks may be impacted by fluency level, but these tasks alone are not direct indicators of fluent or nonfluent characteristics in language dysfunction. Another important distinction is between nonfluent/agrammatic progressive

aphasia in the context of neurodegenerative disease and classic nonfluent aphasia syndromes, typically in the context of stroke (e.g., Broca's aphasia). Nonfluent characteristics from these disparate etiologies have some similarities but are not directly congruent (Patterson, Graham, Ralph, & Hodges, 2006). The second expected impairment, syntax, is an aspect of grammar that refers to sentence structure and word order that conveys a message.

Contrary to the hypothesis, the overall pattern of language dysfunction in the current MND sample did not particularly resemble a nonfluent/agrammatic pattern. However, it is important to note that cases of MND with nonfluent/agrammatic aphasia exist (Bak, O' Donovan, Xuereb, Boniface, & Hodges, 2001; Caselli et al., 1993; De Marchi et al., 2019). Instead, the current preliminary results suggest the nature of language dysfunction in MND is characterized by prominent difficulties with syntax comprehension and/or word retrieval (confrontation naming). Results suggest that these types of language dysfunction may be accompanied by other impairments such as poor verb processing, spelling, and in severe cases impaired repetition with phonemic paraphasias, though these additional difficulties appear to be less common.

Basic verbal comprehension was intact, though difficulties with complex comprehension involving syntax and/or contextual inferences were common. There was not evidence of prominent semantic difficulties, nor was there evidence of perceptual difficulties. When individuals experienced word-finding difficulty, they frequently demonstrated knowledge of the target word through description of the item while trying to produce the word. Though unable to produce the target word spontaneously, word retrieval was frequently aided by phonemic cueing. These performance patterns point to a

primary word retrieval impairment, in the context of intact semantic knowledge and perceptual abilities (Jefferies et al., 2008). Impairments did not appear to be attributable to aging, educational attainment, or premorbid intelligence.

Moreover, results did not necessarily support a prominent nonfluent characteristic that was expected through reduction in expressive language. No patients demonstrated impaired word production during a standardized narrative picture description task. The volume of content-units patients produced about the picture scene was within normal limits (i.e., NAB Oral Production/Writing). Of note, although this picture description task provides objective assessment of word production, the oral version does not assess for other important fluency characteristics such as sentence length and grammar complexity. Therefore, nonfluent characteristics cannot be entirely ruled out in this MND sample. On a qualitative level, speech with empty content (e.g., frequent use of indefinite words such as "they" or "something"), circumlocutions, and simplistic sentence structures were occasionally observed despite normal volume of content-units produced. These qualitative speech observations could hint at mild nonfluent characteristics for some individuals. Additionally, a limited number of participants completed the alternate written version of this task, used for those with loss of speech or significant dysarthria. One case revealed normal conveyance of the scene content but impaired grammar and spelling. In sum, the objective word production assessment did not suggest compromised fluency, though other nonfluent characteristics were not formally assessed and cannot be ruled out.

In nonfluent/agrammatic progressive aphasia, reduced spoken and written word production appears to be more prominent than poor grammar quality (Graham, Patterson,

& Hodges, 2004), which may lend support for absence of nonfluency in this MND sample. However, either reduced speech production *or* agrammatic speech quality satisfy the core diagnostic feature of nonfluent/agrammatic progressive aphasia (Gorno-Tempini et al., 2011).

A small literature suggests nonfluent characteristics may occur in ALS at the level of speech quality rather than word production, though results are inconsistent. Picture narratives from two small ALS samples (*N*s > 27) suggest word production is not significantly reduced when motor speech impairments are taken into account. However, ratings of speech quality revealed worse grammar and discourse including more incomplete sentences, shorter sentences, semantic errors, and less connectedness and theme maintenance (Ash et al., 2014; Ash et al., 2015; Tsermentseli et al., 2016). Conversely, grammatical complexity ratings from the BDAE Cookie Theft picture description task were not significantly different from controls in a larger ALS sample (*N* = 46; Taylor et al., 2013).

Regarding neural correlates, worse grammar was associated with reduced gray matter density in the left inferior prefrontal gyrus[2] [orbital part; Brodmann area (BA) 47], left anterior temporal gyrus (temporal pole; BA 38), left caudate nucleus, and right entorhinal cortex (BA 34; Ash et al., 2015). Worse grammar was also associated with widespread reduced white matter integrity including the: bilateral superior longitudinal fasciculi, cingulum, corpus callosum, right anterior thalamic radiations, left posterior thalamic radiations, bilateral internal capsule, right cerebral peduncle, bilateral uncinate

[2] Verbatim terminology from the authors of the neuroimaging studies are reported. Brodmann areas (BA) are included when reported by the study. Additional descriptive terms are also provided in parentheses at times.

fasciculi, inferior frontal-occipital fasciculi, and right corticospinal tract (Ash et al., 2015). In the same ALS sample, worse speech connectedness was associated with reduced grey matter density in portions of the left inferior frontal gyrus (frontal pole; BA 10), bilateral inferior frontal gyrus (orbital part; BA 47), left orbitofrontal cortex (BA 11), right dorsolateral prefrontal cortex (BA 46), insula, and anterior cingulate (dorsal part; BA 32; Ash et al., 2014). Worse speech connectedness was also associated with reduced white matter integrity including the: right corona radiata, bilateral corpus callosum, right uncinate fasciculus, inferior frontal-occipital fasciculus, and corticospinal tract (Ash et al., 2014).

In contrast, there is converging evidence that when language dysfunction occurs in ALS/MND, it often takes the form of word retrieval and syntax comprehension impairments. These prominent findings parallel results from an unselected group of patients with MND (Rakowicz & Hodges, 1998). Confrontation naming difficulties are also consistent with a growing body of literature (Cobble, 1998; Leslie et al., 2015; Libon et al., 2012; Massman et al., 1996; Taylor et al., 2013; York et al., 2014). During confrontation naming, patients with ALS demonstrate impaired activation in a widespread network of regions including the: right inferior frontal gyrus (dorsolateral prefrontal cortex; BA 46), left inferior frontal gyrus (part of Broca's area; BA 44), right cingulate gyrus (ventral anterior; BA 24), left superior temporal gyrus (Wernicke's area; BA 22), left middle temporal gyrus (BA 37), left middle occipital gyrus (BA 19), and bilateral cuneus (BA 18; Abrahams et al., 2004). However, confrontation naming impairments are unfortunately nonspecific and occur in most aphasia syndromes (Benson & Ardilla, 1996; Rohrer et al., 2008; Stern & White, 2003). Confrontation naming is

variably affected in nonfluent/agrammatic progressive aphasia and not a core feature of this syndrome (Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2011; Migliaccio et al., 2016).

Likewise, convergent research also points to impaired syntax comprehension in MND across different languages (Cobble, 1998; Rakowicz & Hodges, 1998; Taylor et al., 2013; Tsermentseli et al., 2016; Yoshizawa et al., 2014). In ALS, syntax comprehension errors appear to be most common for modifier words that indicate a relationship with another word, known as prepositions in English and particles in Japanese. Passive sentences with modifier words place higher demands on comprehension regarding which noun is executing a verb [e.g., "The girl (*receiving noun*) is given (*verb*) an apple from (*modifier*) the father (*executing noun*)"; Yoshizawa et al., 2014, p. 3].

The neural correlates of syntax comprehension impairments in MND/ALS are unclear. In a small FTD-ALS sample, poorer syntax comprehension was associated with reduced gray matter volume in the right frontal pole, bilateral inferior frontal gyrus, orbitofrontal cortex, left middle frontal gyrus, right medial prefrontal cortex, left insula, paracingulate gyrus, bilateral cingulate, right subcallosal cortex, amygdala, and putamen. This pattern mirrored some regions observed in the nonfluent/agrammatic progressive aphasia group (e.g., left middle and inferior frontal gyri, orbitofrontal cortex, paracingulate gyrus). However, for the ALS only group, syntax comprehension impairments were modest and not significantly correlated with brain volume (Kamminga et al., 2016). Another FTD-MND sample reported similar results: poorer syntax comprehension was associated with expansive frontal cortical regions (e.g., right superior frontal gyrus, bilateral middle and inferior frontal gyri, frontal pole, orbitofrontal cortex),

left insula, several limbic regions (e.g., right paracingulate gyrus, bilateral caudate, left putamen and thalamus), right primary motor and somatosensory cortex, bilateral supramarginal gyrus, and cerebellum (Long et al., 2019).

Together, this literature suggests that prominent language dysfunction features in MND may arise from mild but widespread neuropathology involving frontal (anterior and posterior), temporal, and limbic regions, rather than predominantly focused in the left inferior frontal gyrus and insula (associated with nonfluent/agrammatic aphasia; Gorno-Tempini et al., 2011).

4.1.2 MND/ALSci subgroups.

Patients were classified with MND/ALSci using a comprehensive battery that encompassed both verbal fluency tasks and broader language tests. Consistent with previous research, impaired performance on phonemic fluency tasks was most common (total n = 9; 22.0%), sometimes accompanied by impaired semantic fluency. Under the current consensus criteria, individuals with phonemic fluency impairments are classified with executive dysfunction (Strong et al., 2017). Impaired language affected a similar proportion of the sample (total n = 8; 19.5%). However, these groups were not mutually exclusive.

Three patterns emerged among MND/ALSci with impairments in the language domain and/or verbal fluency. Of those that met criteria for language impairments, all had ALS and demonstrated impaired performance on confrontation naming and/or comprehension tasks that involve syntax. Half of those with language impairments did not meet criteria for phonemic fluency impairments (ALSci-L subgroup n = 4), whereas the other half demonstrated concurrent language and phonemic fluency impairments

(ALSci-L+VF subgroup $n = 4$). The third subgroup were those that met criteria for phonemic fluency impairments, though broader language functioning was relatively intact (MNDci-VF subgroup $n = 5$). This subgroup represented over half of those with impaired phonemic fluency. Interestingly, no patients with PLS had broad language dysfunction, though some had phonemic fluency impairments.

These subgroups could suggest discrete cognitive phenotypes or continua. The ALSci-L+VF subgroup demonstrated similarities with the other two subgroups, overlapping language impairments (i.e., syntax comprehension and/or confrontation naming) and phonemic fluency impairments. Yet, the ALSci-L and MNDci-VF subgroups appeared relatively divergent from one another, language functioning was comparatively intact in the MNDci-VF subgroup. Furthermore, the ALSci-L+VF subgroup appeared more severely impaired compared to the other two subgroups. Impairments within each subgroup also resembled a gradient. Together, these patterns may suggest continua wherein cognitive impairments may first manifest as either executive phonemic fluency impairments (MNDci-VF) or language dysfunction in the form of syntax comprehension and/or confrontation naming impairments (ALSci-L). Plausibly, these focused impairments may progress into a more severe presentation wherein these profiles overlap, and both types of impairments develop (ALSci-L+VF). However, these continua are purely speculative. Longitudinal data would be required to test this hypothesis, whereas the present data are cross-sectional.

4.2 MND Cognitive Screening

The second aim of the study was empirical evaluation of three brief cognitive screens: ALS-CBS, ECAS, and MoCA. Screening sensitivities to broad language

impairments in MND, using the Strong and colleagues consensus criteria (2017), were compared. The ECAS Language subscore was of particular interest, as the only index that targeted language functioning exclusively. Accordingly, it was expected that the ECAS Language subscore would demonstrate the highest sensitivity. Contrary to the hypothesis, the ECAS Language subscore demonstrated the lowest sensitivity to language impairments in the present MND sample. The current preliminary results do not support use of the standard ECAS Language cut-score, which did not perform better than chance-level classification. Recently published demographically adjusted cut-scores (Pinto-Grau et al., 2017) improved overall classification accuracy, which was driven by higher specificity but sensitivity was unchanged. At the sample based point-estimate, the ECAS Language subscore result suggests low sensitivity (50%) to MND/ALSci with language impairments (Strong et al., 2017). Although the upper bound prediction suggests sensitivity could be modest (sensitivity upper bound: 84%). Predictive values indicate potential utility for identifying patients with intact language functioning, but not for those with language impairments (at a base-rate of 19.5%, PPV 29%, NPV 85%; demographically adjusted cut-scores applied per Pinto-Grau et al., 2017).

For ECAS Language, the low point-estimate sensitivity to broad language impairments in the present sample is consistent with low sensitivities to individual confrontation naming and semantic comprehension impairments in a previous study (50% for Boston Naming Test and Pyramids and Palm Trees Test; Pinto-Grau et al., 2017). In contrast, this previous study also reported perfect sensitivity to language impairments defined by combined z-scores from three language tasks that indexed abilities targeted by the ECAS (sensitivity 100%, specificity 83%, PPV 17%, NPV 100%; Pinto-Grau et al.,

2017). The original validation study reported modest classification of language impairments, also defined by combined z-scores (sensitivity 85%, specificity 74%, PPV 33%, NPV 95%), and acknowledged that the ECAS "should be used as a whole test to increase sensitivity and specificity overall" (Niven et al., 2015, p. 176). To my knowledge, the present study is the first to compare the ECAS Language subscale to a gold standard implementing the Strong and colleagues consensus criteria (2017).

The broader ECAS ALS-Specific composite score encompasses screening for verbal fluency, executive functioning, and language impairments. In general, composite screening scores are typically more reliable than subscores. Accordingly, the ECAS ALS-Specific composite score performed better, though sensitivity to language impairments was modest (75%). Specificity to language impairments was low (58%), which is within expectations as the composite score indexes broader cognitive abilities and the criterion assessment focused on language impairments. Results suggest that when using the ECAS, the ALS-Specific composite score should be favored over its subscores.

Unexpectedly, the MoCA (standard or MoCA-BLIND version) performed similarly to the ECAS ALS-Specific composite score, with modest sensitivity to broad language impairments (71%). The MoCA also demonstrated modest specificity (72%) to language impairments in MND. Similarly, specificity is within expectations as the MoCA assesses several cognitive domains and the criterion assessment was language-focused. Chaining the ECAS ALS-Specific composite score with the MoCA resulted in higher sensitivity (88%) but substantially increases administration time for those that undergo both screens, which may reduce the desirability of this method.

Also unexpected, the ALS-CBS, a cognitive screen tailored for executive dysfunction in ALS/MND, demonstrated very high sensitivity to language impairments (100%). Although this result is in the context of a high percentage of impaired ALS-CBS scores within the present sample (73.2%). Specificity to language impairments was low (58%), which is within expectations as the ALS-CBS targets executive functioning. Together these results suggest additional research is warranted regarding ALS-CBS specificity to broader cognitive impairments in MND, which was not addressed by the present language-focused criterion assessment.

Regarding the content of these screens, the ECAS Language items assess confrontation naming, auditory comprehension/semantic access, and spelling. Previous research suggests the ECAS Language subscore is more sensitive to spelling (75%) than other language impairments (Pinto-Grau et al., 2017). Additionally, the ECAS Language subscore was not significantly correlated with syntax comprehension, the most prominent language impairment in this previous sample (i.e., 43.13% PALPA Sentence-Picture Matching; Pinto-Grau et al., 2017). Results from the present study suggests that spelling impairments are less prominent than other forms of language dysfunction in MND (e.g., confrontation naming, syntax comprehension), which may underlie its low sensitivity. The MoCA includes language relevant items that assess naming, sentence repetition, and phonemic fluency. Few naming errors were observed on the MoCA, though sentence repetition in particular may elicit syntax difficulties (e.g., grammar simplification; Goodglass et al., 2001). Furthermore, the ALS-CBS includes a syllable counting item, which may potentially account for the high sensitivity to language impairments observed in the present study. It could be that those with language dysfunction are also likely to

exhibit executive dysfunction assessed within the ALS-CBS. Although this possibility may be less likely as half of those classified with language impairments were not classified with executive phonemic fluency impairments. Alternatively, it is also possible that the ALS-CBS results in a high number of positive test signs overall (i.e., both false positive and true positives), which cannot be determined from the present study.

In summary, brief and accurate cognitive screening in ALS/MND proves challenging, especially for detecting broad language impairments in the cognitive profile. The ECAS includes a targeted language subtest, although the Language subscore did not adequately discriminate language impairments in the present MND sample. In contrast, the ALS-CBS does not directly target language but demonstrated the highest sensitivity to language impairments. However, precise screening for language dysfunction in MND may still call for a language-specific tool. For instance, use of a single full-length language test might be explored as an initial screening tool (see Spreen & Risser, 2003 for a description of this approach).

4.2.1 MND cognitive screening: Convergent and discriminant validity.

Finally, there was evidence of convergent validity between outcomes (i.e., 'impaired' or not) from the two tailored MND cognitive screens, the ALS-CBS and ECAS ALS-Specific composite score. There was also evidence of discriminant validity for the ALS-CBS as compared to the MoCA, a general cognitive screen. Although discriminant validity was not demonstrated for the ECAS ALS-Specific composite score. Results also suggest that screening for broad executive dysfunction primarily underlies differences between the tailored MND screens and the MoCA. In contrast, screening for verbal fluency impairments via the ECAS produced moderate agreement with both the

ALS-CBS and the MoCA, suggesting that these screens result in similar outcomes for these types of impairments.

4.3 Clinical Implications

The present research has several clinical implications. First, disease heterogeneity in MND presents challenges for patient care, treatment, and prognosis. Phenotypic research is crucial to understanding individual differences in disease course. The presence of certain neuropsychological deficits may predict more rapid disease progression (Elamin et al., 2011; Garcia-Willingham et al., 2018). Utilizing phenotypically homogenous MND groups in drug trial designs may reduce error variance and lead to tailored treatments (Benatar et al., 2018). The present study provides further evidence of language dysfunction in MND, which may represent discrete disease subtype(s).

Second, patients with MND often receive many recommendations for supportive care during multidisciplinary clinic visits. The present results highlight the potential for some patients with MND to also develop language impairments, which may impact their ability to process complex verbal information. Thus, it is important for multidisciplinary clinicians to be aware of potential syntax comprehension difficulties in this patient population. For example, patients may have difficulty with complex medication instructions such as "take *at least* 1 hour *before or* 2 hours *after* a meal" (Rilutek package insert; Sanofi-Aventis, 2010). Phrasing instructions in a simple and direct manner is recommended to accommodate patients with potential syntax comprehension difficulties. Providing both written and verbal instructions may also ease cognitive demands on patients. Assessing comprehension by asking patients to restate clinical feedback in their

own words may aid communication and treatment compliance (i.e., the teach-back method; Agency for Healthcare Quality and Research, 2015).

Third, brief cognitive screens are sometimes used in ALS/MND clinics to identify patients with potential impairments for comprehensive evaluation referrals to inform multidisciplinary care. Overall, operating characteristics for detecting language impairments in MND were limited among all brief screens assessed in the present study. When selecting any screening instrument, a decision must be made regarding whether the context calls for more concern with false positives or false negatives. The design of the current study is inherently more concerned with false negatives, with a focus on sensitivity to language impairments in MND. The present results suggest that language impairments in MND are more likely to be detected by the ALS-CBS than the ECAS, though specificity to broader cognitive impairments is uncertain. High false-positive rates are a common problem for screening measures, particularly when the condition prevalence is low (< 50%; Streiner, 2003). The MoCA demonstrated modest sensitivity and specificity to language impairments in the present MND sample, and extensive validation literature supports its use among several other neurodegenerative conditions (e.g., FTD, Huntington's disease, Parkinson's disease; Bezdicek et al., 2013; Freitas et al., 2012; Hoops et al., 2009). At present, given these factors, the MoCA (or MoCA-BLIND) may be a conservative screening option for those with enough functional ability to complete the measure. However, it is important to keep in mind that these cognitive screens do not substitute formal assessment and results should be interpreted with caution (Woolley et al., 2010).

4.4 Limitations

4.4.1 Sampling

The present study intended to sample a representative MND clinic population in the U.S. while accounting for major confounds. Individuals with developmental conditions and educational histories that may bias language performance were excluded (e.g., dyslexia, learning disability, special education). Some evidence exists that individuals with progressive aphasia have higher frequencies of neurodevelopmental learning disabilities, although primarily applicable to the logopenic variant (Miller et al., 2013). However, exclusion was necessary in the present study to avoid misattributing mild premorbid language difficulties to a neurogenerative process. Of note, dementia and mild concussion were not excluded, though moderate to severe TBI was excluded. The present sample reported a high rate of concussion history (49.3%, n = 19), which may be a risk factor for MND (Seelen et al., 2014). However, none were acute and long-lasting impact on language seems unlikely. Excluding concussion would have skewed the sample. Furthermore, although the study was designed to accommodate patients that were unable to speak or unable to write, few patients with bulbar onset or severe dysarthria enrolled in the study. This may limit generalizability to ALS/MND with these presentations and some evidence suggests that syntax comprehension difficulties are more common with bulbar onset (Yoshizawa et al., 2014).

For the portion of the study that examined language dysfunction characteristics, the present sample was powered at 80% to detect a large effect in ALS/MND. However, *a priori* prevalence was underestimated for the portion of the study that examined screening for language impairments. *Post hoc* determinations revealed that at 20%

prevalence, a minimum sample size of 100 patients with MND (including 20 with language impairments) would be required to achieve a minimum power of 80% (actual power = 80.4%) for detecting a change in the *sensitivity* of a screening measure from .50 to .80, based on a target significance level of $p < .05$ (actual $p = .041$; Bujang & Adnan, 2016). Furthermore, at 20% prevalence, a minimum sample size of 25 patients with MND (including 5 with language impairments) would be required to achieve a minimum power of 80% (actual power = 80.4%) for detecting a change in the *specificity* of a screening measure from .50 to .80, based on a target significance level of $p < .05$ (actual $p = .041$; Bujang & Adnan, 2016). Therefore, the present sample did not meet 80% power for sensitivity analyses, but the sample size exceeded the minimum for specificity analyses. Accordingly, the point-estimates for screening sensitivity should be interpreted with consideration to the 95% confidence intervals. However, it is notable that the current sensitivity result for the ECAS Language subscore parallels sensitivities to confrontation naming and semantic comprehension impairments in a recent report, although this study may have been similarly underpowered ($N = 30$; Pinto-Grau et al., 2017).

4.4.2 Assessment

The current language assessment battery was constructed using objective tests with consideration to available standardization data and psychometric properties. Nonetheless, the limitations of the broader language assessment literature also apply to the current assessment. Currently available language tests rarely fulfil recommended psychometric standards (Spreen & Risser, 2003). Researchers have called attention to common weaknesses among language tests such as small standardization samples with limited descriptions and sometimes neglected report of psychometric properties (Harry &

Crowe, 2014; Klein & Buchanan, 2009; Skenes & McCauley, 1985; Spreen & Risser, 2003). However, test properties have improved some with later battery editions and the development of contemporary batteries (Goodglass et al., 2001; Stern & White, 2003).

The current study also aimed to provide a comprehensive language assessment. Nonetheless, certain abilities were partially addressed or not assessed. For example, the assessment included a test of verb processing (i.e., KDT) but did not include verb naming or verb fluency. Evaluation of semantic knowledge was embedded within several tests, without evidence of impairment, though a primary test was not included. Syntax comprehension was also assessed but expressive syntax was not due to lack of assessment tools with standardization data. Notably, adult normative standardization data collection is underway for the Curtiss-Yamada Comprehensive Language Evaluation (CYCLE; Curtiss & Yamada, 2004; personal communication, May 2018), a promising battery that may be useful in future ALS/MND research. Researchers have also emphasized the need for a standardized tool to assess different confrontation naming categories and error types (Harry & Crowe, 2014).

As previously mentioned, the study design focused on language dysfunction but did not include detailed assessment of other cognitive domains. Poor performance on complex comprehension tasks included in the battery (e.g., MAE-3 Token Test, BDAE-3 Complex Ideational Material, and Reading Comprehension Sentences & Paragraphs) could result from various cognitive difficulties such as problems with syntax comprehension, attention, working-memory, short-term memory, motor planning, or global cognitive functioning (Strauss et al., 2006). Therefore, poor language performance

secondary to other impairments cannot be ruled out. Likewise, screening specificities are uncertain for broader cognitive impairments in MND.

4.5 Future Research

Regarding the cognitive profile of MND, the present language dysfunction pattern mirrors some previous research (Rakowicz & Hodges, 1998), though additional replication is warranted. Further evaluation of expressive language, particularly grammar, is also needed. Future research is needed to assess whether language dysfunction and executive dysfunction reflect distinct MND cognitive phenotypes, or whether these impairments evolve together. Research is also needed to evaluate the longitudinal course of language dysfunction in MND, neurodegeneration underlying MND cognitive phenotype(s), and potential relationships with disease progression and prognosis. Yet most crucial, is the fundamental need for psychometrically sound language tests with robust standardization data, as language assessment is becoming increasingly important in MND research.

Regarding brief screening for language dysfunction in MND, one challenge is that numerous types of language impairments exist. However, screens might capitalize on the most common language impairments in this patient population to increase sensitivity and overall accuracy. The present results suggest that naming and syntax comprehension may be fruitful screening targets for future research.

4.6 Conclusion

In conclusion, the present study provides new insight to the cognitive profile of MND with a focus on language. Results suggest the nature of language dysfunction in MND is characterized by prominent difficulties with syntax comprehension and/or word

retrieval (confrontation naming), though other impairments can occur. Previous research implicates a wide network of brain regions associated with language dysfunction in MND. In the present MND sample, 19.5% met Strong and colleagues (2017) MND/ALSci criteria for language impairment. Half of these individuals also met criteria for executive verbal fluency impairment (Strong et al., 2017). Varied cognitive impairments in MND may represent different disease phenotypes. However, brief screening for language impairments remains challenging. The targeted screening tool for language dysfunction in MND (ECAS Language subscore) offered limited classification of broad language impairments in the present MND sample (sensitivity 50%, specificity 70%, PPV 29%, NPV 85%), highlighting the need for additional research in this area.

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Natasha Elsa Garcia-Willingham

VITA

EDUCATION

2015	**M.S., Clinical Psychology, Neuropsychology Track** University of Kentucky, Lexington, KY
2009	**B.A., Psychology with Honors** University of South Florida, Tampa, FL

SCHOLASTIC AND PROFESSIONAL HONORS

2018	University of Kentucky Nominee for the APA Dissertation Research Fellowship
2016	Citation Poster at Annual Meeting of the American Psychosomatic Society
2015	Professional Student Mentored Research Fellowship through the National Center for Advancing Translational Sciences, Dean of the College of Medicine, via internal National Institutes of Health (NIH) grant (UL1TR000117), University of Kentucky
2015	American Psychosomatic Society, Minority Travel Award
2013	Lyman T. Johnson Fellowship
2011	Moffitt Cancer Center Scientific Retreat, Outstanding Poster Award
2010	Moffitt Cancer Center Scientific Retreat, Outstanding Poster Award
2009	University of South Florida Undergraduate Research Symposium, 1st place in the Behavioral Sciences Division

PROFESSIONAL POSITIONS: RESEARCH

July 2018-Present	**Doctoral Candidate Researcher | Language Dysfunction in Motor Neuron Disease: Cognitive Features and Screening Sensitivity** University of Kentucky, Departments of Psychology and Neurology
April 2018-Present	**Graduate Research Assistant | Associations among PTSD, Cognitive Functioning, and Health-Promoting Behaviors in OEF/OIF Veterans** University of Kentucky, Department of Social Work, in collaboration with the Central Texas VAMC, Waco division
July 2013-July 2017	**Graduate Research Assistant | Psychoneuroimmunology Research Lab** University of Kentucky, Department of Psychology
Jan 2017-Dec 2017	**Graduate Research Assistant | Ego Depletion Replication Project** University of Kentucky, Department of Psychology, in collaboration with the University of Minnesota

Feb 2016- Nov 2016	**Graduate Research Assistant | Deep Brain Stimulation for Parkinson's Disease: An Investigation of Post-Surgical Self-Regulation and Cognitive Functioning** University of Kentucky, Departments of Psychology and Neurology
Aug 2011- June 2013	**Clinical Research Coordinator | ALS Research Collaboration Lab** University of Miami Miller School of Medicine, Department of Neurology
Feb 2008- July 2011	**Research Coordinator (promoted from Undergraduate Intern) | Tobacco Research and Intervention Program** University of South Florida, Moffitt Cancer Center

PROFESSIONAL POSITIONS: CLINICAL

March 2015- May 2019	**Adult Assessment Extern | Jesse G. Harris Psychological Service Center** University of Kentucky, Lexington, KY
July 2017- July 2018	**Spinal Cord Unit Extern | Cardinal Hill Rehabilitation Hospital** Lexington, KY
Sept. 2014- Sept. 2017	**Adult Individual Therapist Extern | Jesse G. Harris Psychological Service Center** University of Kentucky, Lexington, KY
Sept. 2016- June 2017	**Neuropsychology Extern | Robley Rex Veterans Affairs Medical Center (VAMC)** Louisville, KY
Feb. 2017- April 2017	**Healthy Relationships Group Leader | Salvation Army Women's Emergency Shelter** Lexington, KY
Sept. 2015- May 2016	**Neuropsychology Extern | Norton Neuroscience Institute** Norton Healthcare, Louisville, KY
Sept. 2015- Nov. 2015	**Mindfulness Group Co-leader | Jesse G. Harris Psychological Service Center** University of Kentucky, Lexington, KY
May 2014- May 2015	**Home Based Primary Care Psychology Extern | Lexington VAMC** Leestown Division, Lexington, KY
Aug. 2013- April 2014	**Psychological Assessment Extern | University of Kentucky** Lexington, KY

PROFESSIONAL POSITIONS: TEACHING

Aug. 2018- May 2019	**Teaching Assistant | University of Kentucky** Personality Psychology, undergraduate 300 level course
Nov. 13th, 2018	**Guest Lecturer | University of Kentucky** Personality Psychology, undergraduate 300 level course

PUBLICATIONS

Wallace, E. R., **Garcia-Willingham, N. E.**, Walls, B. D., Bosch, C. M., Balthrop, K. C., & Berry, D. T. R. (2019). A meta-analysis of malingering detection measures for attention-deficit/hyperactivity disorder. *Psychological Assessment*, *31*(2), 265-270.

Garcia-Willingham, N. E., Roach, A. R., Kasarskis, E. J., & Segerstrom, S. C. (2018). Self-Regulation and Executive Functioning as Related to Survival in Motor Neuron Disease: Preliminary Findings. *Psychosomatic Medicine, 80*(7), 665-672.

Combs, H. L., **Garcia-Willingham, N. E.**, Berry, D. T. R., van Horne, C. G., & Segerstrom, S. C. (2018). Psychological functioning in Parkinson's disease post-deep brain stimulation: Self-regulation and executive functioning. *Journal of Psychosomatic Research, 111,* 42-49.

Scott, A. B., Reed, R. G., **Garcia-Willingham, N. E.**, Lawrence, K. A., & Segerstrom, S. C. (2018). Lifespan Socioeconomic Context: Associations with Cognitive Functioning in Later Life. *The Journals of Gerontology: Series B, 74*(1), 113-125.

Garcia, N. E., Morey, J. N., Kasarskis, E. J., & Segerstrom, S. C. (2017). Purpose in life in ALS patient–caregiver dyads: A multilevel longitudinal analysis. *Health Psychology*, *36*(11), 1092-1104.

BOOK CHAPTER

Garcia, N. E., Bosch, C. M., Walls, B. D., & Berry, D. T. R. (2018). Assessment of feigned cognitive impairment using standard neuropsychological tests. In R. Rogers (Ed.) *Clinical Assessment of Malingering and Deception (4th ed)*.

POSTERS

Wallace, E. R., Balthrop, K. C., Brothers, S. L., Borger, T. N., **Garcia-Willingham, N. E.,** Walls, B. D., & Berry, D. T. R. (2019). "Conners' Adult ADHD Rating Scales–Self-Report: Long Version Infrequency Index validation and pilot comparison of administration formats." Poster at the annual meeting of the International Neuropsychological Society, New York, NY.

Lawrence, K. A., DeBeer, B. B., **Garcia-Willingham, N. E.**, Meyer, E., Kimbrel, N. A., Gulliver, S. B. & Morissette, S. B. (2018). "Does PTSD Moderate the Association between Neuropsychological Functioning and Health Behaviors in Iraq and Afghanistan Veterans?" Poster at the annual meeting of the International Society for Traumatic Stress Studies, Washington, D.C.

Wallace, E. R., **Garcia-Willingham, N. E.,** Walls, B. D., Bosch, C. M., Balthrop, K., & Berry, D. T. R. (2018, February). "A meta-analysis of malingering detection measures for attention deficit/hyperactivity disorder." Poster at the annual meeting of the International Neuropsychological Society, Washington, D.C.

Garcia, N. E., Combs, H. L., Roach, A. R., Anderson, A. J., van Horne, C. G., Berry, D. T. R., & Segerstrom, S. C. (2017, February). "Wisconsin Card Sorting Test subscales in Parkinson's disease and Amyotrophic Lateral Sclerosis." Poster presented at the annual meeting of the International Neuropsychology Society, New Orleans, LA.

Combs, H. L., **Garcia, N. E.,** Berry, D. T. R., & Segerstrom, S. C. (2017, February). "Deep Brain Stimulation for Parkinson's Disease: An Investigation of Post-Surgical Self-Regulation and Executive Functioning." Poster at the annual meeting of the International Neuropsychological Society, New Orleans, LA.

Garcia, N. E., Roach, A. B., Kasarskis, E. J., & Segerstrom, S. C. (2016, March/ 2016, April). "Survival in Motor Neuron Disease: An Analysis of Executive Functioning and Behavior." Poster presented at (1) the annual meeting of the American Psychosomatic Society Conference, Denver, CO, and (2) the University of Kentucky Center for Clinical and Translational Science Spring Conference, Lexington, KY.

Benatar, M., Carlile, R., Reyes, E., Hussain, S., **Garcia, N. E.**, Andersen, P., Stanislaw, C., & Wuu, J. (2015, April). "Models of ALS Disease Onset and Progression: Insights from the Pre-fALS Study." Annual meeting of the American Academy of Neurology, Washington, D.C.

Garcia, N. E., Kasarskis, E. J., & Segerstrom, S. C. (2015, March/ 2015, March). "Purpose in Life in ALS Patient-Caregiver Dyads: Effects of Disease Progression." Poster presented at (1) the annual meeting of the American Psychosomatic Society, Savannah, GA, and (2) Kentucky Psychological Foundation Spring Academic Conference, Midway, KY.

Garcia, N. E., & Segerstrom, S. C. (2014, March). "Five-Factor Personality Dimensions Correlate with Different Cognitive Abilities Among Older Adults." Poster presented at the annual meeting of the American Psychosomatic Society, San Francisco, CA.

Garcia, N. E., Combs, H. L., & Segerstrom, S. C. (2014, February). "Practice Effects and Longitudinal Change in Processing Speed and Executive Functioning Among Older Adults." Poster presented at the annual meeting of the International Neuropsychology Society, Seattle, WA.

Combs, H. L., **Garcia, N. E.**, Segerstrom, S. C. (2014, February). "Age and IQ Moderate Practice Effects of Verbal Memory Ability in Older Adults." Poster at the annual meeting of the International Neuropsychology Society, Seattle, WA.

Garcia, N. E., Ornduff, R. D., Oliver, J. A., Drobes, D. J., & Evans, D. E. (2011, February / 2011, March). "Effects of Nicotine versus Placebo on N-back Performance in Smokers." Poster presented at (1) the annual meeting of the Society for Research on Nicotine and Tobacco, Toronto, ON. (2) Updated poster presented at the Moffitt Cancer Center Scientific Retreat, Tampa, FL.

Ornduff, R. D., **Garcia, N. E.,** Oliver, J. A., Drobes, D. J., & Evans, D. E. (2011, February). "Nicotine Effects on Vigilant Attention and Working Memory among Nonsmokers*."* Poster at the annual meeting of the Society for Research on Nicotine and Tobacco, Toronto, ON.

Ditre, J., Oliver, J. A., **Garcia, N. E.,** Evans, D. E., & Drobes, D. J. (2010, October). "Emotional Reactivity and Divalproex: Independence of Autonomic and Somatic Systems." Poster at the annual meeting of the Society for Psychophysiological Research, Portland, OR.

Evans, D. E., Ornduff, R. D., **Garcia, N. E.,** Park, J. Y., & Drobes, D. J. (2010, October). "An ERP index of Attentional Bias to Negative Affect Words among Smokers." Poster presented at the annual meeting of the Society for Psychophysiological Research, Portland, OR.

Garcia, N. E., Oliver, J. A., Elibero, A., & Drobes, D. J. (2009, February / 2010, March). "Effects of Yoga and Cardiovascular Exercise on Cue Reactivity while Attempting Smoking Cessation." Poster presented at (1) the University of South Florida Undergraduate Research Symposium, Tampa, FL. (2) Updated poster presented at the Moffitt Cancer Center Scientific Retreat Poster Session, Tampa, FL.

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