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Physical frailty in late-life depression is associated with deficits in speed-dependent executive functions

Guy G. Potter¹, Douglas R. McQuoid¹, Heather E. Whitson^{2,3}, and David C. Steffens⁴

¹Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC

²Center for the Study of Aging and Human Development, Duke University Medical Center

³Durham VA Medical Center Geriatrics Research Education and Clinical Center (GRECC)

⁴Department of Psychiatry, University of Connecticut Health Center, Farmington, CT

Abstract

Objective—To examine the association between physical frailty and neurocognitive performance in late-life depression (LLD).

Methods—Cross-sectional design using baseline data from a treatment study of late-life depression. Individuals aged 60 and older diagnosed with Major Depressive Disorder at time of assessment (N = 173). All participants received clinical assessment of depression and completed neuropsychological testing during a depressive episode. Physical frailty was assessed using an adaptation of the FRAIL scale. Neuropsychological domains were derived from a factor analysis that yielded three factors: 1) Speeded Executive and Fluency, Episodic Memory, and Working Memory. Associations were examined with bivariate tests and multivariate models.

Results—Depressed individuals with a FRAIL score >1 had worse performance than nonfrail depressed across all three factors; however, Speeded Executive and Fluency was the only factor that remained significant after controlling for depression symptom severity and demographic characteristics.

Conclusions—Although physical frailty is associated with broad neurocognitive deficits in LLD, it is most robustly associated with deficits in speeded executive functions and verbal fluency. Causal inferences are limited by the cross-sectional design, and future research would benefit from a comparison group of nondepressed older adults with similar levels of frailty. Research is needed to understand the mechanisms underlying associations among depression symptoms, physical frailty, and executive dysfunction, and how they are related to the cognitive and symptomatic course of LLD.

Keywords

geriatric depression; late-life depression; frailty; executive dysfunction; neuropsychological

Please address correspondence to: Guy G. Potter, PhD, Psychiatry, Box 3903, Duke University Medical Center, Durham, NC, 27710-3903, fax: 919-681-7668, phone: 919-668-1269, guy.potter@duke.edu.

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INTRODUCTION

Major Depressive Disorder (MDD) is estimated to be the 3rd highest contributor to global disease burden, and the highest among middle- and high-income countries (World Health Organization, 2008). When depression occurs roughly after age 60, described as late-life depression (LLD), it is often accompanied by neurocognitive deficits, and this co-occurrence is associated with worse treatment response (Potter *et al.*, 2004, Story *et al.*, 2008, Alexopoulos *et al.*, 2000), greater disability (Potter *et al.*, 2012a, Kiosses *et al.*, 2001), and increased risk of dementia (Potter *et al.*, 2012b). Neurocognitive deficits in LLD also appear more intractable to treatment than other depression features, as remitted individuals demonstrate persistently worse neurocognitive performance compared to nondepressed individuals (Bhalla *et al.*, 2006, Lee *et al.*, 2007, Kohler *et al.*, 2010). Thus, a critical strategy to reduce the health burden of LLD involves identifying factors associated with its neurocognitive deficits.

One potential contributor to neurocognitive deficits in LLD is frailty. The clinical syndrome of frailty characterizes older individuals at increased risk for adverse health outcomes including disability and morbidity. Frailty is believed to occur from declines across multiple physiological systems that fail to respond adequately to stressors (Abellan Van Kan *et al.*, 2008a). There is currently no consensus definition of frailty. Leading definitions characterize frailty as a physical phenotype for underlying biological decline (Fried *et al.*, 2001), an outcome of accumulated deficits, (Rockwood and Mitnitski, 2007), or a loss of capability across functional domains (Strawbridge *et al.*, 1998). Despite a lack of consensus, these definitions of frailty are correlated and predict similar outcomes of disability and mortality (Cigolle *et al.*, 2009, Rockwood *et al.*, 2007, Malmstrom *et al.*, 2014).

Research has shown that frailty and depression often co-occur. Increasing odds of frailty have been associated with increased depression symptoms in older adults (St John *et al.*, 2013), and frailty has been associated with incidence and persistence of depression symptoms (Makizako *et al.*, 2014, Feng *et al.*, 2014). It has been argued that the combination of high depression symptoms and cerebrovascular burden is a prodrome for frailty (Paulson and Lichtenberg, 2013), while a recent review found empirical support for a bidirectional association between depression and frailty in later life (Mezuk *et al.*, 2012). Nonetheless, frailty and LLD appear to be distinct syndromes despite overlapping elements (Mezuk *et al.*, 2013).

There is growing attention in the research literature to the association between frailty and cognitive deficits, as many of the age-associated processes that lead to frailty also contribute to unhealthy brain aging. Frailty has been associated with cognitive decline using both biological and deficit accumulation models (Mitnitski *et al.*, 2011), including outcomes of mild cognitive impairment and dementia (Boyle *et al.*, 2010, Song *et al.*, 2011, Solfrizzi *et al.*, 2013). While there are consistent associations between frailty and lower global cognitive function with screening-type measures (Avila-Funes *et al.*, 2009, Rockwood *et al.*, 2007), studies using more extensive neurocognitive testing have tended to find that frailty is most strongly associated with information processing speed and speed-dependent executive functions (e.g., timed outcomes), and is less frequently associated with episodic memory,

working memory, and visuospatial skills (Boyle *et al.*, 2010, Langlois *et al.*, 2012, Patrick *et al.*, 2002, Rolfson *et al.*, 2013, Lin *et al.*, 2014). The associations between frailty and cognition have led to the inclusion of cognitive impairment in some definitions of frailty (Sternberg *et al.*, 2011); however, we share the position of Robertson and colleagues (Robertson *et al.*, 2013) that while physical frailty and age-related cognitive impairment have bidirectional influences and shared risk factors, they are distinct and nonoverlapping constructs.

There is limited research examining frailty, depression, and neurocognition together, which is an important gap in the research literature because of the prevalence of neurocognitive deficits in LLD, and because these deficits lead to adverse morbidity and disability outcomes similar to frailty. While broad neurocognitive deficits have been found in LLD, several studies suggest that performances on neuropsychological measures of processing speed mediate the differences between depressed and nondepressed older adults on other neuropsychological domains (Butters *et al.*, 2004, Nebes *et al.*, 2000, Sheline *et al.*, 2006). It is also potentially important to consider age of first depression onset, based on findings from some studies that neurocognitive deficits may be greater among individuals with first onset of MDD occurring later in life (Mackin *et al.*, 2014, Sachs-Ericsson *et al.*, 2013). To the best of our knowledge, no prior studies have examined the association between frailty and neurocognitive function in LLD. A neurocognitive phenotype for frailty in LLD would be a useful marker for detecting individuals at greater risk of adverse outcomes of depression, and better understanding the links between frailty, cognitive impairment, and LLD may lead to better approaches to preventing and treating all three conditions.

The objective of the current study was to identify whether there is a unique association of physical frailty to neurocognitive performance in active LLD, and to better determine the neurocognitive domains that are associated with it. Our hypothesis was that actively depressed individuals who exhibit characteristics of physical frailty would demonstrate worse neurocognitive performance overall compared to nonfrail individuals with LLD, and that the strongest association would exist in the domain of speed-dependent executive functions. The test of our hypothesis assumes the association between frailty and neurocognitive performance will remain significant after controlling for related clinical and demographic variables.

Methods

Participants

All participants were enrolled in the Neurocognitive Outcomes of Depression in the Elderly study (NCODE; Steffens *et al.*, 2004). All individuals were 60 years or older with a diagnosis of major depressive disorder at the time of enrollment. Diagnoses were assigned by study-trained psychiatrists using standardized assessment instruments and diagnostic algorithms. Assessment included the Duke Depression Evaluation Schedule (DDES; Landerman *et al.*, 1989), which includes psychiatric assessments, as well as self report of functional performance and medical conditions used in the current operational definition of frailty. Exclusion criteria at the time of enrollment included: 1) another major psychiatric illness; 2) alcohol or drug abuse or dependence; and 3) primary neurologic illness, including

clinical stroke and dementia. Individuals were screened for dementia at time of enrollment based on an established protocol that included review of a comprehensive clinical evaluation, consultation with referring physicians, and cognitive screening with the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975). Individuals whose baseline MMSE scores remained below 25 after an acute eight-week phase of treatment were not followed longitudinally.

Research with participants was conducted in accordance with the Helsinki Declaration (World Medical Association, 2013), and this study was approved by the Duke University Institutional Review Board.

Frailty Assessment

Our frailty variable was adapted from the FRAIL scale (Abellan Van Kan *et al.*, 2008b, Morley *et al.*, 2012). The FRAIL scale was developed by the Geriatric Advisory Panel of the International Academy of Nutrition and Aging for use as a case-finding tool, and as a measure that could be readily used with clinical patients. It combines elements of biological, deficit accumulation, and functional domain definitions of frailty (Malmstrom *et al.*, 2014, Abellan Van Kan *et al.*, 2008b), and has demonstrated construct and predictive validity (Woo *et al.*, 2012, Morley *et al.*, 2012, Ravindrarajah *et al.*, 2013). The original FRAIL scale includes domains of: 1) Fatigue (“Are you fatigued?”), 2) Resistance (Cannot walk up 1 flight of stairs?”), 3) Aerobic (“Cannot walk 1 block?”), 4) Illnesses (“Do you have more than 5 illnesses?” [as read from list]), and 5) Loss of weight: (“Have you lost more than 5% of your weight in the past 6 months?”). The presence or absence of each item is defined dichotomously, and the total score is the sum of items present. For the purposes of the current study, we used analogs of the FRAIL items from our clinical assessment data. Fatigue was adapted from CES-D items 7 and 20, which are the same items used in Fried *et al.*’s biological definition (“I felt that everything I did was an effort”; “I could not ‘get’ going”). Resistance was based on DDES self-reported ability to walk up and down a flight of stairs without resting. Aerobic was based on DDES self-reported ability to walk a quarter of a mile, or approximately 3 city blocks. Illnesses was based on self-reported endorsement of 5 out of 10 illnesses assessed by the DDES that are comparable to the FRAIL scale (asthma, diabetes, heart trouble, hypertension, arthritis/rheumatism, cancer, emphysema, ulcers, hardening of the arteries, other chronic physical health problem). Loss of weight was defined by CES-D item 2 pertaining to appetite loss. Because we had no reliable measure of weight loss in the current study, we used appetite loss as a proxy indicator of nutritional compromise or cachexia, similar to the approach taken in the SHARE study (Santos-Eggimann *et al.*, 2009).

Neuropsychological Assessment

Participants completed a neuropsychological assessment battery at the time of study enrollment. Participants were tested by a trained psychometrician using standardized administration and scoring procedures for each test. There were 13 tests included: 1) CERAD Word List Learning (Welsh *et al.*, 1994), 2) CERAD Word List Delayed Recall (total correct), 3) Logical Memory I and 4) Logical Memory II (Wechsler, 1987), 5) Benton Visual Retention Test (Sivan, 1992), 6) Symbol-Digit Modalities Test (Smith, 1982), 7) Part

A and 8) Part B of the Trail Making Test (Reitan, 1992), 9) Animal Naming, 10) Controlled Oral Word Association (Benton and Hamsher, 1988), 11) Forward, and 12) Backward subtests of Digit Span (Wechsler, 1997), and 13) Ascending Digit Span (Sair *et al.*, 2006). Scores for each measure were based on total correct responses, with the exception of Trail Making, which was time to complete (reverse scored).

We used factor analysis to reduce the 13 neuropsychological measures to a smaller set of variables. Common factor analysis was performed with SAS Proc Factor (SAS Institute, 2012), using principal component extraction, varimax rotation to produce orthogonal factors, and factor scores from SAS Proc Score. To optimize factor stability, we used the full cohort of NCODE depressed participants ($n = 327$). The additional participants were those who did not have all frailty-related data required for the current study, but who otherwise met the same study entry criteria. The individuals only included for factor analysis ($n = 154$) differed from the current study sample with respect to a higher proportion of women in the total cohort compared to the current sample, $\chi^2(1) = 4.40$, $p = 0.04$. A variable for gender ("sex") was included subsequent regression models as a covariate. Eigenvalues greater than 1.0 and a scree plot were used to determine the number of factors. To facilitate interpretation, we weighted our consideration toward items with factor loadings ≥ 0.50 (Table 1): Factor 1 was interpreted as reflecting Speeded Executive and Fluency (SEF), Factor 2 was interpreted as Episodic Memory (EM), Factor 3 was interpreted as reflecting Working Memory (WM).

Statistical Methods

Statistical analysis included examination of descriptive statistics, and testing of group differences using chi-square tests, Student's *t*-tests, and Satterthwaite's approximate test. We planned multivariate regression models to formally test the relationship between frailty and neurocognition while controlling for demographics, depression severity, and onset of depression. Age of depression onset was obtained from the DDES as a self-report of age of first depression onset. As there may be some variability recalling a specific chronological age of first depression onset (Blazer, 2003), we dichotomized the variable with a cutpoint of age 60. We estimated one model for each neurocognitive domain score, in which the neurocognitive domain score was the dependent variable, and a dichotomous variable for frailty was entered as an independent variable in the model with the covariates. Prior research on the FRAIL in nondepressed samples defined prefrail status as FRAIL = 1–2 (Morley *et al.*, 2012, Woo *et al.*, 2012), but this may overdiagnose frailty in LLD due to the high prevalence of Fatigue (82%) in actively depressed older adults. To account for this, we examined the distribution of frailty scores in the sample, and designated the nonfrail group to include adapted FRAIL scores of 0–1, and the frail group to subsume prefrailty and include adapted Frail scores of 2–5. *A priori* covariates included age, years of education, sex, race (Caucasian/non-Caucasian), age of depression onset, and depression severity. Depression severity was based on the sum of the CES-D *minus* items 2, 7, and 20 that were used in the operational definition of frailty. A p -value < 0.05 indicated statistical significance.

RESULTS

Frail individuals were older, had fewer years of education, were more depressed, were more often women, and were more often non-Caucasian (Table 2). Age of first depression onset did not differ between groups. Bivariate tests for group differences between frailty and neurocognitive performance indicated that individuals with frailty performed worse on all three neurocognitive factors, and on 10 out of 13 individual neurocognitive tests (Table 2).

The results of the multivariate regression models found that SEF was the only neurocognitive factor significantly associated with frail status when controlling for covariates. Because age, race, gender, and years of education were also associated with frail status and may serve as possible moderators, we ran separate models testing for interactions between these variables and frailty. None of the interaction terms were statistically significant.

DISCUSSION

This study found that community-dwelling older adults with active MDD and physical frailty demonstrated worse neurocognitive performance than a comparison group of active MDD without frailty. Although the frail individuals with LLD had lower performance than the nonfrail LLD participants across all three neurocognitive factors assessed, the Speeded Executive and Fluency domain had the only unique association with frailty, based on multivariate models controlling for demographic characteristics and depression severity. Neurocognitive factors were associated with covariates of age (SEF, EM, WM), education (SEF, EM, WM), race (SEF, WM), sex (EM), and age of depression onset (EM), but not with overall depression severity, and there were no significant interactions between any of these covariates and frailty. To our knowledge, this is the first study to examine multi-domain neurocognitive performance and frailty in clinically diagnosed MDD, and includes the novel finding that frailty is associated with unique variance in speed-dependent executive function performance. Thus, even among older adults who have been robustly characterized as clinically depressed, a physical/somatic frailty scale is useful in distinguishing people with different neurocognitive profiles.

Our finding that frailty in LLD was more strongly associated with a speed-dependent executive factor relative to other neurocognitive factors is consistent with findings in non-clinical samples (Robertson *et al.*, 2013), including research suggesting depression symptoms and frailty indicators (gait speed) may represent a phenotype of aging associated with cognitive slowing and/or executive dysfunction (Hajjar *et al.*, 2009). It also highlights the importance of information processing speed to the profile of neurocognitive deficits in LLD (Nebes *et al.*, 2000, Butters *et al.*, 2004, Sheline *et al.*, 2006). The inclusion of verbal fluency in the SEF factor is consistent with the clinical use of verbal fluency tests to assess aspects of executive function (Lezak *et al.*, 2012), and with research showing that executive functions and cognitive speed contribute to verbal fluency performance in older adults (Shao *et al.*, 2014). Much as motor slowing is a core feature of physical frailty (Fried *et al.*, 2001), slowed thought may be core feature of cognitive frailty.

A major clinical implication of this study is that frailty in LLD is associated with broad neurocognitive deficits and psychomotor-executive function in particular, which is a marker for poor treatment response (Sheline *et al.*, 2012, Potter *et al.*, 2004, Alexopoulos *et al.*, 2005) and functional limitations in LLD (Romero-Ortuno and Soraghan, 2014, Gobbens and Van Assen, 2012). Physical and cognitive impairments may challenge adherence, self-management, and access to care. Thus, persons with LLD who exhibit frailty characteristics may benefit from additional resources and services and merit more thorough cognitive evaluation. Frailty in LLD is also associated with increased mortality (Buchman *et al.*, 2009); in fact, one study found that increased mortality associated with active depression was itself strongly influenced by frailty (Almeida *et al.*, 2014). In light of research suggesting that frailty is associated with adverse outcomes in LLD, interventions to reduce or remediate frailty symptoms in older adults, such as addressing diet and physical inactivity, may be helpful in reducing incident depression as well as minimizing persistent cognitive and functional limitations among individuals who experience an active episode of MDD. Based on our findings and those in the broader aging literature (Fried *et al.*, 2001), clinical attention to frailty may be particularly important among women and African Americans. In particular, the FRAIL scale appears well-suited to clinical use (Morley *et al.*, 2012).

The current study has limitations, but ones which may provide directions for future research. Because our study design was cross-sectional, we cannot identify any temporal associations among mood, frailty, and cognition, which limits insight into causal mechanisms. Causal mechanisms are important to address in future research, in light of evidence for predisposing and bidirectional influences of frailty in LLD (Mezuk *et al.*, 2013). The mean age of our sample could be considered “young-old.” We do not know how our findings would generalize to an “old-old” sample, but given the increased prevalence of frailty and cognitive decline with age (Jacobs *et al.*, 2011), we expect greater convergence of neurocognitive dysfunction and frailty in older LLD samples. Our study also did not include a nondepressed comparison sample. Though potentially challenging to identify, future research on frailty in LLD would benefit from a nondepressed comparison group with low depression symptoms and a representative range of frailty.

Another limitation to the current study may exist in our operational definition of frailty. To our knowledge, this is the first study to examine frailty and neurocognitive function in the context of active clinically diagnosed MDD, and the parent study was not designed to include specific measures of physical performance like grip strength or gait speed. We selected a scale based on clinical information and designed our operational definition of frailty to be as close to the FRAIL scale as possible using available data. As noted by King-Kallimanis and colleagues (King-Kallimanis *et al.*, 2014), frailty definitions are frequently opportunistic, and they argue it is reasonable to assume overlap when commonalities exist in the definition. Given that different definitions of frailty have been shown to converge (Lohman *et al.*, 2015, Malmstrom *et al.*, 2014), we do not expect that our operational definition of frailty would produce results that are substantially different from alternative definitions. The clinical definition of frailty used in the current study limits our ability to draw conclusions with respect to specific theoretical models (e.g., biological vs. deficit

accumulation) or common underlying mechanisms, such as cerebrovascular disease (Paulson and Lichtenberg, 2013). These are directions for future research.

We also recognize a potential confound to studying frailty in MDD when defining a criteria of the two conditions overlap. This overlap is inherent in many operational definitions of frailty, including the biological (CES-D items 7 and 20; Fried *et al.*, 2001) and deficit accumulation models (mental/emotional problems; Rockwood and Mitnitski, 2007). Unlike most studies, our participants were actively depressed based on established clinical diagnostic criteria, so our question addressed whether frailty in the context of MDD was associated with greater neurocognitive deficits, above and beyond the effects of overall depression severity. Our results indicated that greater frailty in the context of active MDD was associated with worse SEF performance, and we believe this was not confounded by depression-frailty overlap. On the broader question of overlap between depression and frailty, we agree with the position that depression and frailty are distinct conditions with overlapping components that suggest common underlying mechanisms and risk factors (Mezuk *et al.*, 2013, Lohman *et al.*, 2015). Further study of these mechanisms and risk factors is warranted.

Another possible limitation is that participants were enrolled in a naturalistic treatment study designed to optimize individual treatment response. Thus, as a group, individuals were treated with several different psychotropic medications and combinations thereof. In this respect, our sample is more similar to the general population of depressed older adults treated in their community than are samples from single-agent trials, but it does limit the ability to control for potential effects of type and quantity of medication, which may contribute to frailty (Lakey *et al.*, 2012). We examined total number of medications and total number of antidepressants among our sample, and found no associations with neurocognitive performance. Thus, we believe it unlikely that medication differences would have a systematic effect on neurocognitive performance, which is consistent with previous studies (Siepmann *et al.*, 2003, Podewils and Lyketsos, 2002).

CONCLUSION

In conclusion, the presence of frailty in LLD is uniquely associated with worse performance on a neurocognitive factor reflecting speeded executive function and verbal fluency. Additional research is needed to more fully understand the shared and distinct characteristics of frailty and LLD and how these are related to mechanisms underlying executive dysfunction.

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Key point

Physical frailty is a unique contributor to executive dysfunction in late-life depression

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Table 1

Results of factor analysis for neurocognitive measures

	Factor		
	SEF	EM	WM
SDMT	0.7640	0.3108	0.2362
TMT-A (reversed)	0.7395	0.3510	0.2122
TMT-B (reversed)	0.7326	0.1974	0.0550
Animal Naming	0.7092	0.2653	0.1492
COWA	0.7053	0.0237	0.2476
BVRT	0.5891	0.4694	0.2046
LM I	0.2160	0.8978	0.0856
LM II	0.2318	0.8932	0.1128
WLM-D	0.2587	0.6407	0.2883
WLM-I	0.2718	0.5905	0.3828
DS-F	0.1226	0.1535	0.8313
DS-B	0.2646	0.1958	0.7851
DS-A	0.4759	0.2348	0.4759
Eigenvalue	6.2947	1.2569	1.0647
Variance explained (%)	27.44	23.36	15.48

Note. Factor loadings >0.50 indicated in bold. SEF = Speeded Executive and Fluency. EM = Episodic Memory. WM = Working Memory. TMT = Trail Making Test (reverse scored for factor analysis). SDMT = Symbol-Digit Modalities Test. COWA = Controlled Oral Word Association. BVRT = Benton Visual Retention Test. WLM-I = CERAD Word List Memory-Immediate. WLM-D = CERAD Word List Memory –Delayed. LM = Logical Memory. DS-F = Digit Span Forward. DS-B = Digit Span Backward. DS-A = Digit Span Ascending.

Table 2

Demographic and clinical characteristics associated with frailty

	Nonfrail (n = 89) M (SD)	Frail (n = 84) M (SD)	Statistic <i>t</i> (df), or χ^2 (df)
Age	67.47 (5.75)	69.07 (6.85)	$t(171) = 1.67$
Years education	14.75 (2.21)	13.69 (2.85)	$t(156.63) = 2.73^b$
% female	47.19%	69.05%	$\chi^2(1) = 8.46^b$
% Caucasian	87.64%	75.00%	$\chi^2(1) = 4.58^a$
Age of first depression onset (% > 60)	20.22%	26.19%	$\chi^2(1) = 0.87^{ns}$
CES-D	26.75 (11.51)	33.85 (8.47)	$t(161.55) = 4.63^b$
CES-D, adj.	22.93 (10.24)	27.35 (7.43)	$t(160.57) = 3.26^b$
MMSE	28.29 (1.79)	27.58 (1.96)	$t(171) = 2.48^a$
Modified FRAIL items			
Fatigue	71.91% (64)	96.43% (81)	$\chi^2(1) = 19.15^b$
Resistance	3.37% (3)	54.76% (46)	$\chi^2(1) = 56.22^b$
Aerobic	1.12% (1)	26.19% (22)	$\chi^2(1) = 23.56^b$
Illness	0.00% (0)	15.48% (13)	$\chi^2(1) = 14.89^b$
Loss	3.37% (3)	65.48% (55)	$\chi^2(1) = 74.79^b$
Neurocognitive factor scores			
SEF	0.29 (0.88)	-0.28(0.97)	$t(171) = 4.04^b$
EM	0.15 (0.88)	0.10 (0.92)	$t(171) = 0.37^{ns}$
WM	0.10 (0.92)	-0.14 (1.03)	$t(171) = 1.58^{ns}$
Neurocognitive raw scores (highest factor loading)			
TMT-A (SEF)	38.91 (18.59)	47.99 (23.29)	$t(158.71) = 2.82^b$
TMT-B (SEF)	99.54 (55.8)	141.9 (74.6)	$t(153.46) = 4.20^b$
SDMT (SEF)	41.38 (10.12)	34.70 (11.26)	$t(171) = 4.11^b$
Animal Naming (SEF)	18.17 (4.52)	15.82 (4.44)	$t(171) = 3.44$
COWA (SEF)	36.71 (11.64)	32.02 (12.21)	$t(171) = 2.58^a$
BVRT (SEF)	6.28 (1.67)	5.54 (2.07)	$t(159.47) = 2.59^a$
WLM-I (EM)	19.60 (4.16)	18.71 (3.97)	$t(171) = 1.42^{ns}$
WLM-D (EM)	6.82 (1.96)	6.33 (1.86)	$t(171) = 1.68^{ns}$
LM I (EM)	25.70 (7.02)	24.05 (7.57)	$t(171) = 1.49^{ns}$
LM II (EM)	21.97 (7.82)	20.12 (8.44)	$t(171) = 1.49^{ns}$
DS-F (WM)	8.94 (2.24)	7.83 (2.41)	$t(171) = 3.14^b$
DS-B (WM)	7.10 (2.14)	6.65 (2.27)	$t(171) = 1.33^{ns}$
DS-A (WM)	8.80 (2.40)	8.02 (2.68)	$t(171) = 2.00^a$

^a
 $p < .05$

^b
 $p < .01$.

^{ns}
= not significant.

Note. CES-D = Center for Epidemiologic Studies Depression Scale. CES-D adj.= adjusted sum of CES-D items, *excluding* those that are used to define Frailty (items 2, 7, 20). TMT = Trail Making Test (higher values reflect slower performance). SDMT = Symbol-Digit Modalities Test. COWA = Controlled Oral Word Association. WLM-I = CERAD Word List Memory-Immediate. WLM-D = CERAD Word List Memory-Delayed. LM = Logical Memory. DS-F = Digit Span Forward. DS-B = Digit Span Backward. DS-A = Digit Span Ascending.

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Table 3

Multivariate regression models of frailty status predicting neurocognitive factors, with covariates

Factors	SEF			EM			WM		
	B	η^2	p	B	η^2	p	B	η^2	p
Frail	-.33	0.02	0.02	0.08	0.00	0.57	-.13	0.00	0.39
Age	-.03	0.03	<0.01	-.02	0.02	0.04	0.03	0.03	0.02
Sex	0.02	0.00	0.88	-.27	0.02	0.05	0.11	0.00	0.49
Race	-.40	0.02	0.02	-.26	0.01	0.13	-.52	0.04	<0.01
Onset	-.00	0.00	0.70	-.01	0.03	0.02	-.01	0.01	0.17
Educ.	0.13	0.11	<0.01	0.08	0.05	<0.01	0.07	0.03	0.02
CES-D, adj.	-.00	0.00	0.98	-.01	0.01	<0.19	0.00	0.00	0.81
F	10.30			4.63			3.83		
R ²	0.30			0.16			0.14		
Model p			<0.01			<0.01			<0.01

Note. SEF = Speed Executive/Fluency, EM = Episodic Memory, WM = Working Memory. For Frailty, Frail = 1. For Sex, female = 1. For Race, Caucasian = 1. For Age of first depression onset, $< 60 = 1$. Educ. = Years of education. CES-D adj. = adjusted sum of CES-D items, *excluding* those that are used to define Frailty (items 2, 7, 20).