THE GERONTOLOGICAL SOCIETY OF AMERICA®

*Journals of Gerontology: Medical Sciences*
cite as: *J Gerontol A Biol Sci Med Sci*, 2020, Vol. 75, No. 9, e67–e73
doi:10.1093/gerona/glz287
Advance Access publication December 12, 2019

OXFORD

Research Article

# Longitudinal Association Between Perceived Fatigability and Cognitive Function in Older Adults: Results from the Baltimore Longitudinal Study of Aging

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Received: June 4, 2019; Editorial Decision Date: December 3, 2019

**Decision Editor:** Anne Newman, MD, MPH

## Abstract

**Background:** Cognitive decline is consistently associated with diminished life satisfaction and inability to live independently. Identifying early, novel markers of cognitive decline is imperative for improving clinical detection and promoting long-term quality of life. Fatigability, one's perceived exertion after a standardized walking task, has been associated with declines in physical function; however, it remains unclear as to whether these effects may also extend to cognitive function.

**Methods:** We examined whether perceived fatigability, assessed as the rating of perceived exertion (RPE) after a 5 min slow-paced treadmill walk (0.67 m/s, 0% grade), is longitudinally associated with cognitive performance in the domains of memory, executive functions, language, and attention among 934 cognitively intact individuals aged at least 50 years participating in the Baltimore Longitudinal Study of Aging (BLSA); $M_{age}$ = 69.6 ± 10.1, 51.9% female participants. Continuous associations between RPE and each domain (individual test and composite scores) were assessed using linear mixed-effect models adjusted for demographics and comorbid conditions.

**Results:** In fully adjusted models, higher fatigability at baseline was associated with declines in all cognitive domains over an average 2.2 years of follow-up ($p < .04$ for all). Longitudinally, increased fatigability over time was associated with worsened executive functions (β= –0.01, $p = .002$).

**Conclusions:** These findings suggest that perceived fatigability after a standardized walking task may aid in identification of individuals at a higher risk of future cognitive decline. Future research should examine underlying biological mechanisms contributing to this relationship as well as whether future interventions may target fatigability in midlife to attenuate age-related cognitive decline.

**Keywords:** Cognition, Fatigability, Perceived exertion

Declines in cognitive functioning occur with aging, even in the absence of dementia (1). Domains of higher order cognition, such as episodic memory, executive functions, fluid abilities, and processing speed, are the last to fully develop but the first to exhibit decay (2–4). Despite an overall trend of decline with age in these domains, cognition may be malleable throughout adulthood, involving both gains and losses partly attributable to certain lifestyle behaviors (eg, physical activity, environment enrichment, cardiovascular health (5–7)). Understanding correlates of cognitive decline, such as fatigue and health behaviors, may thus inform the development of lifestyle interventions to maintain brain health and improve independence and life satisfaction into old age (8,9).

Fatigue has been highlighted as an early indicator of poor outcomes with aging (10) that may place older adults at increased risk

of disability and mortality (11). Moreover, older adults with higher fatigue have demonstrated poorer cognitive function (12), and a greater propensity for physical frailty and associated cognitive decline (13). However, despite this evidence, the magnitude of the association between fatigue and cognitive decline is not well defined, as fatigue can be difficult to measure given its subjectivity and contextual dependence (14). Thus, there is an increased need for measurement tools that adequately characterize fatigue in the context of aging and cognition.

Perceived fatigability is a construct designed to assess fatigue through perceived effort or exertion after a standardized task (15,16). Distinct from fatigue, which can be defined as a self-reported sensation, fatigability is a complex construct that incorporates the perception of fatigue after a standardized activity (eg, timed slow walk), removing self-pacing bias (16). Well-validated in older populations (17,18), fatigability is emerging as an increasingly useful tool that complements traditional functional and behavioral measures for ultimately discriminating health and functional status (14).

Increasing evidence suggests that cognitive deficits, particularly those at the subclinical level, may first manifest through deterioration of subcortical tracts that connect the brain to the musculature (19). Given that coordination of musculoskeletal movement and goal-directed motor performance is initiated by the brain, fatigability may thus be an early marker of brain dysfunction foreshadowing the onset and progression of cognitive decline. Accordingly, this study examines the association between both baseline and change in perceived fatigability and longitudinal change in multiple domains of cognitive functioning among cognitively normal participants in the Baltimore Longitudinal Study of Aging (BLSA), a large, prospective study of older adults. It was hypothesized that individuals with higher levels of fatigability at baseline and increased fatigability over time would exhibit greater annual declines in cognitive function across domains, even after accounting for demographics, education, and comorbidities.

## Materials and Methods

### Participants and Study Design

The BLSA is a study of normative human aging, established in 1958 and conducted by the National Institute on Aging Intramural Research Program. A general description of the sample and enrollment procedures and criteria has been previously reported (20,21). Briefly, the BLSA is a continuously enrolled cohort with some targeted recruitment (eg, women, racial minorities) over its 60 year history. All participants are community-dwelling volunteers who passed comprehensive health and functional screening evaluations and were free of major chronic conditions and cognitive and functional impairment at the time of enrollment. Once enrolled, participants are followed up for life and continue to undergo extensive testing every 1–4 years depending on age (<60: every 4 years, 60–79: every 2 years, ≥80: every year).

The sample for the current study consists of 934 men and women at least 50 years of age who underwent physical examinations, health history assessments, and cognitive and functional testing repeatedly between August 2007 and December 2015. Participants were evaluated at research diagnostic case conferences if they scored 0.5 or greater on the Clinical Dementia Rating scale or if they had more than 3 errors on the Blessed-Information-Memory Concentration Test. Individuals meeting criteria for mild cognitive impairment or dementia were excluded from analyses after onset of clinical impairment ($n$ = 17) (22). The Internal Review Board of the National Institute of Environmental Health Sciences approved the study protocol and participants provided written informed consent at every study visit.

### Measures

#### Demographics and Covariates

All participants completed a physical examination and health history assessment. Age, sex, race, and total years of education were self-reported. Weight and height were measured according to standard protocols and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m$^2$). The presence of chronic conditions was assessed by nurse practitioners and established according to information on medical history, drug treatment, and physical examination. Chronic conditions included in the analysis were: cardiovascular disease (history of heart disease or cardiac surgery, including myocardial infarction, congestive heart failure, angina, coronary artery bypass, peripheral artery disease, and angioplasty), cerebral vascular disease (history of stroke or transient ischemic attack), pulmonary disease (history of chronic bronchitis, emphysema, chronic obstructive pulmonary disease, or asthma), liver disease (cirrhosis or liver disease), kidney disease (self-reported diagnosis of kidney disease, nephritis, or renal insufficiency), diabetes (self-reported past diagnosis and current medication for diabetes), neuropathy (self-reported peripheral neuropathy or nerve damage in lower legs, feet or hands), hypertension (systolic blood pressure ≥140 or diastolic blood pressure ≥90 or treatment with antihypertensive drugs), cancer (self-reported history of nonskin cancer), and arthritis (self-reported past diagnosis of lower extremity arthritis pain). Presence (1 = yes, 0 = no) across chronic conditions was summed to create a total comorbidities score. Covariates were compiled a priori based on previous literature linking fatigue and cognition in the context of aging (12,16).

### Cognitive Measures

*Executive functions* were assessed using the Digit Span Backward subtest of the Wechsler Adult Intelligence Scale—Revised (WAIS-R) (23), the Trail Making Test (TMT) Part B (24), the Digit Symbol Substitution Test (DSST) (23), and a difference score representing the difference in time to complete (in seconds) Trails B compared with Trails A (Delta TMT) (25,26). The domain scores of executive functions were computed using the average of the standardized $z$ scores from the Digit Span Backward and the TMT Part B tests. *Memory* was assessed using immediate and long free recall from the California Verbal Learning Test (CVLT) (27), and the domain scores of memory were computed using the average of the standardized $z$ scores of these two measures. *Language* was assessed using Verbal fluency—letters (28) and Verbal fluency—categories (29), and the domain scores of language were computed using the average of these standardized $z$ scores. *Attention* was assessed using TMT Part A and the Digit Span Forward subtest of the WAIS-R (23,24), and the domain scores of attention were computed using the average of the standardized $z$ scores.

For the test-specific scores, Digit Span Forward and Backward, DSST (range 0–94), CVLT immediate and long recall, and the fluency measures, higher values indicate better performance. TMT Parts A and B variables represent total time to complete the tasks measured in seconds, where higher values indicate slower task time and thus worse performance.

### Fatigability

Perceived fatigability was assessed immediately after 5 min of slow treadmill walking at 0.67 m/s (1.5 mph) and 0% grade by asking participants to rate their perceived exertion using the Borg rating of perceived exertion (RPE) scale (range 6–20; 6 = no exertion at all, 9 = very light, 11 = light, 13 = somewhat hard, 20 = maximal exertion) (30). A single speed was used for all participants, providing a standardized measure by which to gauge age-related differences in fatigability. A speed of 0.67 m/s was selected to be low demand to minimize participant exclusion at the higher end of the age spectrum (31). Perceived fatigability has been previously evaluated for criterion and predictive validity (17,32), demonstrating greater promise than other measures of fatigue in older adults. The first participant visit at which fatigability was measured is defined as "baseline fatigability" for clarity throughout the paper; however, it should be noted that this is a prospective cohort study with ongoing recruitment.

### Data Analysis

Linear mixed-effect (LME) models with cognitive measures or domain scores at each occasion as separate outcomes were used to assess the association between: (i) baseline perceived fatigability and change in cognitive functioning and (ii) longitudinal changes in perceived fatigability and change in cognitive functioning. Time was calculated as years from each participant's baseline fatigability assessment. Change in fatigability was calculated as the difference between fatigability at baseline and at each subsequent timepoint. To assess the associations in (i) and (ii) above, we fit both unadjusted models (Model 1) and fully adjusted models (Model 2). The fixed effects for unadjusted models included baseline fatigability, change in fatigability and interaction terms between time and baseline fatigability and change in fatigability and time. Built on the unadjusted model, the fixed effects for fully adjusted models included baseline age, sex, race, years of education, number of morbid conditions, and BMI. The random effects in all models included intercept and time with an unstructured covariance. All LME models were estimated using restricted maximum likelihood (REML) method. Initial lowess plots and model fit testing suggested that our linear association assumption between fatigability and cognition was warranted; therefore fatigability (independent) variables were modeled continuously. Baseline fatigability was centered on its minimum value, 6. Baseline age was centered on 70 years and modeled continuously along with years of education, number of morbid conditions, and BMI. Sex was dummy coded with 0 as female and 1 as male, whereas race was coded with 0 as nonwhite and 1 as white. In a subset of participants, sensitivity analyses explored the inclusion of apolipoprotein 4 (APOE4) genotype ($n$ = 923) and depression ($n$ = 926) as covariates. These variables were not significant and removed from the final model to preserve model fit and parsimony. Missing data were minimal (<5%) and thus treated as missing at random. Significance level for all models was set to 0.05 and all analyses were conducted using Stata version 15.1 (StataCorp, College Station, Texas).

## Results

Participant characteristics are detailed in Table 1. Briefly, individuals in the current study were on average 70 ($SD$ = 10.1) years of age at baseline, mostly Caucasian (66.4%), and well-educated (~17 years of education) with few chronic conditions (60.8% had 0–1). The racial makeup of the non-Caucasian sample was 27.2% African American, 3.9% Asian, and 2.5% other. The most common morbid conditions at baseline were hypertension (43.8%) and lower extremity arthritis pain (35.7%). Participants were followed up for an average of 2.2 (±2.3) years (range: 0–8.2); 70% of participants had more than one visit, 44% had more than three visits, and 21% had more than four visits. Individuals with two or more visits were followed for an average of 4.5 (±1.9) years (range: 0.9–8.2). Individuals with one visit only contributed to the estimates of the baseline effects in the LMEs. Unadjusted (Model 1) and fully adjusted (Model 2) longitudinal results are displayed in Tables 2 (domains) and 3 (individual test scores).

**Table 1.** Baseline Demographics, Health, and Cognitive Characteristics of Participants From the Baltimore Longitudinal Study of Aging (BLSA)

| | Mean (SD) or $n$ (%) |
|---|---|
| Variable | Total sample ($n$ = 934) |
| Age (years) | 69.6 (10.1) |
| Female | 485 (51.9%) |
| Caucasian | 620 (66.4%) |
| Body mass index | 27.3 (4.6) |
| Years of education | 16.8 (2.7) |
| Years of follow-up (all) | 2.21 (2.3) |
| Range (min–max) | 0–8.2 |
| Years of follow-up (≥2 visits) | 4.5 (1.9) |
| Range (min–max) | 0.9–8.2 |
| Number of morbid conditions | |
| 0–1 | 568 (60.8%) |
| ≥2 | 366 (39.2%) |
| Baseline fatigability | 8.69 (2.4) |
| WAIS-R Digit Span Forward Total Score | 8.07 (2.4) |
| WAIS-R Digit Span Backward Total Score | 6.89 (2.4) |
| WAIS-R Digit Symbol Substitution Test | 45.9 (11.4) |
| Trail Making Test—Part A | 32.5 (12.6) |
| Trail Making Test—Part B | 82.7 (41.5) |
| Trail Making Test—Delta(B – A) | 50.5 (36.5) |
| CVLT—immediate recall | 51.4 (12.1) |
| CVLT—long recall | 10.9 (3.3) |
| Verbal fluency—categories[a] | 16.0 (3.7) |
| Verbal fluency—letters[a] | 14.3 (4.2) |

Note: WAIS-R = Wechsler Adult Intelligence Scale—Revised; CVLT = California Verbal Learning Test.

[a]Summed scores across three trials.

### Memory

Baseline fatigability was associated with subsequent annual memory decline [Table 2, β= −0.01, $p$ = .01], after controlling for age, sex, race, BMI, years of education, number of morbid conditions, and change in fatigability. Change in fatigability over time was not associated with changes in memory ($p$ = .27). When exploring the individual tests comprising the memory domain [Table 3], baseline fatigability was negatively associated with immediate recall on the CVLT [β= −0.13, $p$ < .001]; however, there was no relationship between baseline fatigability and CVLT long delay free recall ($p$ = .26). Increased fatigability over time was not associated with annual declines in immediate or long delay recall on the CVLT ($p$s > .22).

### Executive Functions

Higher baseline fatigability was associated with declines in executive functions [Table 2, β= −0.00, $p$ = .04] after full covariate adjustment. Additionally, increases in fatigability were associated with

**Table 2.** Linear Mixed Effect Models of the Association of Baseline Fatigability and Longitudinal Change in Fatigability with Change in Cognitive Domains Over Time

| | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|
| | β (SE) | *z* | *p* | β (SE) | z | *p* |
| Memory (*n* = 910) | | | | | | |
| Change in Fatigability[a] × Time | −.00 (.00) | −1.10 | .27 | −.00 (.00) | −1.11 | .27 |
| Baseline Fatigability × Time | −.01 (.00) | −2.75 | .01* | −.01 (.00) | −2.67 | .01* |
| Time[b] | −.00 (.01) | −0.24 | .81 | −.00 (.01) | −0.37 | .71 |
| Executive functions (*n* = 906) | | | | | | |
| Change in Fatigability × Time | −.01 (.00) | −3.06 | .002* | −.01 (.00) | −3.06 | .002* |
| Baseline Fatigability × Time | −.01 (.00) | −2.20 | .03* | −.00 (.00) | −2.01 | .04* |
| Time[b] | −.01 (.01) | −1.85 | .07 | −.02 (.01) | −2.03 | .04* |
| Language (*n* = 921) | | | | | | |
| Change in Fatigability × Time | −.00 (.00) | −0.65 | .51 | −.002 (.003) | −0.68 | .50 |
| Baseline Fatigability × Time | −.00 (.00) | −2.53 | .01* | −.004 (.002) | −2.44 | .02* |
| Time[b] | −.01 (.01) | −2.09 | .04* | −.01 (.01) | −2.09 | .04* |
| Attention (*n* = 918) | | | | | | |
| Change in Fatigability × Time | −.00 (.00) | −1.34 | .18 | −.01 (.00) | −1.45 | .15 |
| Baseline Fatigability × Time | −.01 (.00) | −2.88 | .004 | −.01 (.00) | −2.73 | .01* |
| Time[b] | −.01 (.01) | −0.89 | .37 | −.01 (.01) | −1.07 | .28 |

Note: Model 1: unadjusted; Model 2: fully adjusted for interaction main effects (change in fatigability, baseline fatigability, and time), age, sex, race, years of education, comorbidities, and body mass index.

[a]Fatigability units are in rating of perceived exertion total score: sample range 6–19.

[b]Time is interpreted when change in fatigability = 0, baseline fatigability = 6, and age = 70.

*$p < .05$.

annual declines in executive functions [β= −0.01, $p = .002$]. For the individual tests underpinning the executive functions domain, baseline fatigability was associated with declines in performance for the TMT Part B [Table 3, β = 0.33, $p = .02$], but not for Digit Span Backward ($p = .37$). Increased fatigability was associated with annual declines in Digit Span Backward [β= −0.03, $p = .01$] and TMT Part B [β = 0.46, $p = .04$].

Fatigability was also associated with other tests of executive functions not included in the domain. Both higher baseline and increased fatigability were associated with annual declines in the DSST [Table 3, β= −0.06, $p = .02$; β= −0.10, $p = .01$, respectively]. No associations were found for either baseline or change in fatigability and Delta TMT ($p$s > 0.10).

### Language

Similar to the memory domain, baseline fatigability, but not increased fatigability over time, was associated with annual declines in language [Table 2, β= −0.004, $p = .02$], after full covariate adjustment. For the tests comprising the language domain, higher baseline fatigability was associated with annual declines in letter fluency [Table 3, β= −0.02, $p = .02$]. There was no association between change in fatigability and letter fluency ($p = .78$) or fatigability and category fluency ($p$s > .11).

### Attention

Higher baseline fatigability was associated with annual decline in attention [Table 2, β= −0.01, $p = .01$] after full adjustment, but change in fatigability over time was not ($p = .15$). Similarly, only higher baseline fatigability was associated with increased time to complete TMT Part A [Table 3, β = 0.17, $p = .01$]. For the Digit Span Forward subtest of WAIS-R, there were no associations between either baseline fatigability or change in fatigability over time ($p$s > 0.23).

## Discussion

Our findings identify longitudinal associations between perceived fatigability and a variety of cognitive domains in older adults. Specifically, higher levels of fatigability at baseline were associated with declines in all cognitive domains, even after controlling for potential confounders, and increased fatigability over time was associated with a decline in executive functions. To the best of our knowledge, this is the first analysis to explore the association between perceived physical fatigability and cognitive functioning in older adults. Our results suggest that the detection of excess perceived physical fatigability may aid in identification of individuals at a higher risk of future cognitive decline.

These findings are timely considering the burgeoning interest in identifying and attenuating cognitive decline in a growing population of older adults. We previously reported that perceived fatigability remains relatively stable over a mean of 2 years of follow-up in well-functioning older adults (18), which may explain the more robust associations between baseline fatigability and subsequent cognitive functioning relative to longitudinal change in fatigability. These differential effects have significant implications for the development of screening tools and interventions targeting cognitive health in old age. The ability to assess fatigability at a single time point may provide healthcare professionals with a fast and efficient method of risk stratifying individuals for both physical (32) and cognitive decline. Importantly, these findings are within the context of a prospective, observational study with no attempt to change fatigability. It therefore remains unclear if interventions designed specifically to improve fatigability would subsequently result in improved cognition.

Currently, we lack intervention strategies for fatigability, making it increasingly important to better understand how fatigability fits into the complex interplay of psychosocial and biological hallmarks of the aging process, and more specifically, why fatigability may be linked to cognitive domains as evidenced in the current study. It is

**Table 3.** Linear Mixed Effect Models of the Association of Baseline Fatigability and Longitudinal Change in Fatigability with Change in Cognitive Test Scores Over Time

| | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|
| | β (SE) | *z* | *p* | β (SE) | *z* | *p* |
| *Memory* | | | | | | |
| CVLT immediate recall (*n* = 912) | | | | | | |
| Change in Fatigability[a] × Time | −.06 (.05) | −1.21 | .23 | −.06 (.05) | −1.23 | .22 |
| Baseline Fatigability × Time | −.13 (.03) | −3.84 | <.001* | −.13 (.03) | −3.74 | <.001* |
| Time[b] | .15 (.11) | 1.36 | .17 | .15 (.11) | 1.31 | .19 |
| CVLT long recall (*n* = 910) | | | | | | |
| Change in Fatigability × Time | −.01 (.02) | −0.59 | .56 | −.01 (.02) | −0.60 | .55 |
| Baseline Fatigability × Time | −.01 (.01) | −1.21 | .23 | −.01 (.01) | −1.13 | .26 |
| Time[b] | −.05 (.03) | −1.57 | .12 | −.06 (.03) | −1.81 | .07 |
| *Executive functions* | | | | | | |
| Trails Part B (*n* = 907) | | | | | | |
| Change in Fatigability × Time | .42 (.23) | 1.85 | .06 | .46 (.23) | 2.04 | .04* |
| Baseline Fatigability × Time | .37 (.14) | 2.56 | .01* | .33 (.14) | 2.28 | .02* |
| Time[b] | .32 (.48) | 0.68 | .50 | .40 (.47) | 0.85 | .40 |
| Delta TMT (*n* = 906) | | | | | | |
| Change in Fatigability × Time | .34 (.22) | 1.51 | .13 | .37 (.22) | 1.66 | .10 |
| Baseline Fatigability × Time | .22 (.14) | 1.57 | .12 | .17 (.14) | 1.27 | .20 |
| Time[b] | .30 (.45) | 0.66 | .51 | .39 (.45) | 0.87 | .39 |
| Digit Span Backward (*n* = 926) | | | | | | |
| Change in Fatigability × Time | −.03 (.01) | −2.52 | .01* | −.03 (.01) | −2.51 | .01* |
| Baseline Fatigability × Time | −.01 (.01) | −1.02 | .31 | −.01 (.01) | −0.90 | .37 |
| Time[b] | −.04 (.03) | −1.33 | .19 | −.04 (.03) | −1.55 | .12 |
| DSST (*n* = 906) | | | | | | |
| Change in Fatigability × Time | −.09 (.04) | −2.35 | .02* | −.10 (.04) | −2.54 | .01* |
| Baseline Fatigability × Time | −.07 (.03) | −2.45 | .01* | −.06 (.03) | −2.41 | .02* |
| Time[b] | −1.06 (.09) | −12.04 | <.001** | −1.03 (.09) | −11.55 | <.001** |
| *Language* | | | | | | |
| Verbal fluency—categories (*n* = 922) | | | | | | |
| Change in Fatigability × Time | −.02 (.01) | −1.33 | .18 | −.02 (.01) | −1.37 | .17 |
| Baseline Fatigability × Time | −.02 (.01) | −1.66 | .10 | −.02 (.01) | −1.59 | .11 |
| Time[b] | −.16 (.03) | −4.84 | <.001** | −.15 (.03) | −4.81 | <.001** |
| Verbal fluency—letters (*n* = 921) | | | | | | |
| Change in Fatigability × Time | .00 (.02) | 0.29 | .77 | .00 (.02) | 0.28 | .78 |
| Baseline Fatigability × Time | −.02 (.01) | −2.46 | .01* | −.02 (.01) | −2.44 | .02* |
| Time[b] | .07 (.03) | 2.05 | .04* | .06 (.03) | 1.93 | .05 |
| *Attention* | | | | | | |
| Trails Part A (*n* = 919) | | | | | | |
| Change in Fatigability × Time | .09 (.08) | 1.10 | .27 | .11 (.08) | 1.37 | .17 |
| Baseline Fatigability × Time | .19 (.07) | 2.77 | .01* | .17 (.07) | 2.59 | .01* |
| Time[b] | −.12 (.22) | −0.54 | .59 | −.12 (.22) | −0.52 | .60 |
| Digit Span Forward (*n* = 926) | | | | | | |
| Change in Fatigability × Time | −.01 (.01) | −0.60 | .55 | −.01 (.01) | −0.63 | .53 |
| Baseline Fatigability × Time | −.01 (.01) | −1.31 | .19 | −.01 (.01) | −1.20 | .23 |
| Time[b] | −.03 (.03) | −1.11 | .27 | −.04 (.03) | −1.36 | .18 |

Note: Model 1: unadjusted; Model 2: adjusted for interaction main effects (change in fatigability, baseline fatigability, and time), age, sex, race, years of education, comorbidities, and body mass index; CVLT = California Verbal Learning Test.; TMT = Trail Making Test; DSST = Digit Symbol Substitution Test.

[a]Fatigability units are in rating of perceived exertion total score: sample range 6–19.

[b]Time is interpreted when change in fatigability = 0, baseline fatigability = 6, and age = 70.

*$p < .05$.

**$p < .001$.

possible that fatigue perceptions originate in areas of the brain that, when deteriorated, contribute to a loss in inhibition of how one perceives their physical fatigue. Recent cross-sectional work has indicated associations between physical fatigability and brain structures, specifically the hippocampus, putamen, thalamus, basal ganglia, and limbic system (33), suggesting that physical fatigability may have a neurobiological component. The hippocampus is well-known for its critical relationship with memory (34), whereas the putamen and thalamus are known for regulating movement (35) and relaying sensory impulses (36), respectively. It seems reasonable that such structures (and their related cognitive processes) might be associated with perceived fatigability. Speed of processing has also been associated with these brain regions and plays a key role in several of the neuropsychological measures employed herein (eg, attention, language

fluency, and executive functions); thus, it may also underlie fatigability. There is a need for future research to longitudinally assess the complex relationships between fatigability, cognitive processing, and brain imaging over a longer follow-up to better understand the underlying mechanisms and ultimately preserve cognitive health.

No associations were detected between change in fatigability and the memory, language or attention domains. Although potentially due to the stability of perceived fatigability over time in this cohort (18), this finding may simply reflect a more robust association between fatigability and executive functions. The attention domain also included Trails Part A, generally considered the "easier" task of the Trail Making Test paradigm as it does not tap the complex processing required in Part B (eg, switching between sets). Trails Part A may thus be more indicative of impaired motor performance than true cognitive deficits. It is also possible that fatigability does not follow fatigue's association with cognitive processing through autonomic processing (37), but rather through higher ordering thinking such as executive functions. Interestingly, associations were observed for some but not all tests within a single cognitive domain. Domains, such as executive functions, exhibit both diversity and unity (38), and cognitive tests have shared underlying neural pathways (ie, speed of processing) between domains in addition to tapping distinct pathways. Future research should expand on these relationships using other measures of these cognitive domains to further elucidate the extent of the fatigability association.

These findings should be considered within the context of their strengths and weaknesses. To the best of our knowledge, no study to date has examined the association between perceived physical fatigability and cognition. The current analysis provides a unique perspective on fatigue perceptions anchored to a standardized task and their relationship with cognitive function in older age. Similarly, few studies examining the prospective relationship between fatigue and cognition have used the objective cognitive measures employed herein to quantitatively assess changes in cognitive outcomes over time, opting instead for self-reported measures or screening tools (39). Although such measures are easy to disseminate with low participant and researcher burden, they may be inadequate for capturing clinical change (40,41). This analysis also expands on the paucity of research in large samples examining the longitudinal relationship between subjective measures of fatigue and cognitive function in older adults (42).

It should be noted that BLSA volunteers are relatively healthy older adults with exceptionally high educational attainment who are cognitively intact at enrollment, thus limiting the generalizability of the current results. It is nevertheless exciting to see such robust associations evidenced in healthier participants whose cognitive test scores are well above a level that would be cause for concern, making it important to replicate these findings in more heterogeneous samples and clinical populations, with higher levels of fatigability and poorer overall cognitive ability. It might be expected that these associations would be magnified in those who are clinically impaired, either cognitively or physically. Finally, it remains unknown whether the associations evidenced in the current sample represent a clinically meaningful change in cognitive functioning, which may be partly due to a shorter follow-up time (mean 2.2 years). This leaves us unable to make conclusions about fatigability's long-term relationship to cognitive change; however, we should note that the mean follow-up for individuals with two or more assessments was 4.5 years. Declining cognition is widespread with increasing age for which we are unable to control in our models, but these findings represent a first pass at understanding how fatigability may act as a potential early risk indicator of cognitive decline in old age. Future research is warranted to better understand how changes in midlife fatigability may influence cognition several decades later as individuals transition into old age.

Maintaining and enhancing cognition in older adulthood remains a critical public health goal in the United States as the population of older adults continues to grow. The findings presented herein highlight fatigability as a potentially sensitive risk indicator of accelerated cognitive decline. Screening tools and interventions designed to target fatigability earlier in life may represent an exciting opportunity to further research toward modifying the trajectory of cognitive decline, thereby delaying dementia onset.

## Funding

This work was supported in part by the Intramural Research Program, National Institute on Aging at the National Institutes of Health; and the National Institute on Aging at the National Institutes of Health (U01AG057545, R21AG053198, P30AG021334) to J.A.S.

## Acknowledgments

E.A.S., J.A.S., L.F., E.M.S., and S.M.R. were involved in the study conception, design, and/or experimental protocol; E.A.S., A.A.W., E.M.S., J.A.S., L.F., S.M.R., Y.A., and J.K.U. performed or oversaw the collection of and/or analysis of data; E.A.S., J.A.S., and A.A.W. wrote the manuscript and all authors provided critical review of the final version of the manuscript.
*Conflicts of interest statement*: None declared.

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