Physiologic Dysfunction Scores and Cognitive Function Test Performance in United States Adults

Roni W Kobrosly, MPH[1],[*], **Christopher L Seplaki, PhD**[1], **Courtney M Jones, MPH**[1], and **Edwin van Wijngaarden, PhD**[1]

[1]Department of Community and Preventive Medicine, University of Rochester Medical Center. Rochester, New York, United States.

Abstract

Objective—To investigate the relationship between a measure of cumulative physiologic dysfunction and specific domains of cognitive function.

Methods—We examined a summary score measuring physiological dysfunction, a multisystem measure of the body's ability to effectively adapt to physical and psychological demands, in relation to cognitive function deficits in a population of 4511 adults aged 20 to 59 who participated in the third National Health and Nutrition Examination Survey (1988–1994). Measures of cognitive function comprised three domains: working memory, visuomotor speed, and perceptual-motor speed. 'Physiologic dysfunction' scores summarizing measures of cardiovascular, immunologic, kidney, and liver function were explored. We used multiple linear regression models to estimate associations between cognitive function measures and physiological dysfunction scores, adjusting for socioeconomic factors, test conditions, and self-reported health factors.

Results—We noted a dose-response relationship between physiologic dysfunction and working memory (coefficient = 0.207, 95% CI = (0.066, 0.348), p < 0.0001) that persisted after adjustment for all covariates (p = 0.03). We did not observe any significant relationships between dysfunction scores and visuomotor (p = 0.37) or perceptual-motor ability (p = 0.33).

Conclusions—Our findings suggest that multisystem physiologic dysfunction is associated with working memory. Future longitudinal studies are needed to clarify the underlying mechanisms and explore the persistency of this association into later life. We suggest that such studies should incorporate physiologic data, neuroendocrine parameters, and a wide range of specific cognitive domains.

Keywords

Allostatic Load; Cognition; Epidemiology; Cross-Sectional Analysis

[*]Corresponding Author: Roni W. Kobrosly, Department of Community and Preventive Medicine, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Box 644, Rochester, New York 14642 United States. Tel: 1-585-276-4840; Fax: 1-585-461-4532, Roni_Kobrosly@URMC.Rochester.edu.

CONFLICTS OF INTEREST

The authors confirm that there are no conflicts of interest to declare.

INTRODUCTION

Epidemiologic research has examined late-life, individual demographic, socioeconomic, and physiologic factors associated with cognitive performance and decline in multiple neurological domains. Research addressing the physiologic correlates of cognition focuses on its links with cardiovascular, hepatic, renal, and endocrine systems(1–10). Dysregulation of blood pressure, including both orthostatic hypotension and hypertension, has been persistently associated with diminished cognitive function, above and beyond sociodemographic and additional medical factors(4, 6). Additionally, other cardiovascular disease risk factors (e.g., elevated BMI, history of diabetes)(9, 10), prior history of stroke (2), elevated systemic inflammation(3, 5), and decreased kidney and liver function (1, 4, 7, 8) have all been associated with lower cognitive performance in older adults. Furthermore, it is known that some of these biological parameters are dynamically interrelated (in particular, the cardiovascular, metabolic, and inflammatory parameters) (11). These findings suggest that a measure of overall physiological dysfunction, integrating cardiovascular risk factors and various biological parameters of declining physical health, may be an even stronger correlate of cognitive function than risk factors considered in isolation.

The allostatic load model proposed by McEwen and Stellar integrates these different biological parameters into one unifying framework that may be particularly useful in predicting cognitive decline (12, 13). This model details how continual adaption to demands and stimuli over the life course may damage the body's response system and associated physiological functioning, potentially resulting in dysfunction or disease of many body systems including (but not limited to) cardiovascular, renal, and hepatic systems(12–15). Fundamentally, allostasis is the physiologic process by which the human body responds and adapts to acute and chronic stressors through activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the release of physiologic mediators of adaptation, such as cortisol(12, 15). The allostatic load model provides a framework for examining biological "wear and tear" and has been operationalized in a wide range of recent epidemiologic studies(16–19).

The relationship between a global measure of cumulative physiologic dysfunction and specific domains of cognitive function has rarely been empirically evaluated. A study of 765 high functioning elderly subjects (age 70–79 years) noted cross-sectional associations between a physiological dysfunction summary score (comprising 10 biomarkers of physiologic activity) with memory, spatial ability, and abstract reasoning deficits(20). This physiological dysfunction summary score was guided by the allostatic load model(14, 15). A recent study of 195 adolescents (mean age 17.3 years) noted how higher childhood allostatic load predicted deficits in adolescent working memory(21). Another epidemiologic study reported that heart rate recovery, blood pressure, and cortisol response patterns, constituting cumulative physiologic dysregulation, were associated with poorer memory in 133 elderly adults (mean age 70.6 years)(22). These studies suggest that physiologic dysfunction may be associated with cognitive status in adults of all ages. However, these studies did not rely on nationally-representative samples and did not examine the impact of physiologic dysfunction on early to mid-life adult cognitive performance.

The mechanisms to explain the association between cumulative physiologic dysfunction and cognitive performance are complex and likely vary with different domains of cognitive function. However, one potential explanation can be inferred through endocrine system dysregulation(13, 23). A recent analysis demonstrated that the endocrine disruption that drives allostatic load is statistically explained by multiple domains of physiologic dysfunction, including the cardiovascular, metabolic, and immune systems(13). Endocrine system dysfunction can be described through the collective functioning of these various

bodily systems, as the HPA-axis exerts direct effects on all organs and tissues of the body(24). Thus, simultaneous elevation of leukocytes levels, blood pressure, heart rate, as well as abnormal serum lipid profiles and abnormal markers of hepatic and renal function is likely to signal dysfunction of the HPA-axis(15, 24).

The HPA-axis endocrine cascade affects glutamatergic transmission in synapses involving glutamate receptor subunits in the pre-frontal cortex (PFC) (25). The PFC is thought to be crucial in the deployment of short-term memory(26). In addition, it has also been suggested that hippocampal plasticity, a function critical in learning, is affected by endocrine hormones of the HPA-axis(27). Physiologic dysfunction (including cardiovascular, immunologic, kidney, and liver function) is thought to reflect HPA-axis dysregulation that could result in diminished cognitive performance. Because it has been shown that physiologic dysfunction accumulates from early adulthood onward(16), it is plausible that cognitive performance among early or middle-age adults could be associated with physiologic dysfunction.

Nevertheless, the etiology of cognition in early to mid-life adults is an understudied phase in the trajectory of cognitive functioning across the life course(28, 29). In addition, while existing studies have generally investigated associations between specific domains of physiologic functioning and global or general cognition, there is a gap in the literature in our understanding of linkages between overall physiologic dysfunction and specific domains of cognition. It is imperative to address this gap because the various unique domains of cognition exhibit different associations with age, sociodemographic factors, and environmental factors(30). Improvements in our understanding of interconnected physiologic and cognitive processes among early to mid-life adults may provide additional insights into age-related physiological decline among older adults and may expand targets for intervention to maintain cognitive function (28, 31).

We address this gap by exploring the association between measures of specific domains of cognitive function and two different scores summarizing measures of cardiovascular, immunologic, kidney, and liver function, among adults of age 20–59 years, in the third National Health and Nutrition Examination Survey (NHANES), a nationally representative, multistage survey. We adjusted for a range of sociodemographic factors, test-performance-related factors, and specific health indicators, which were selected based on an assessment of prior literature. Given prior evidence of a link between HPA-axis activity and learning and memory ability(32), we hypothesize that a summary score measuring physiological dysfunction, as conceptualized through the allostatic load model, will be negatively associated with working memory performance.

METHODS

NHANES III Methods and Study Population

NHANES III (1988 – 1994) is a cross-sectional, probability survey of the non-institutionalized, civilian United States population aged one to 90 years. The sampling procedures and study protocols are discussed at length elsewhere(33). The National Center for Health Statistics institutional review board approved the NHANES III protocols and informed consent was obtained from all participants.

The third cycle of NHANES occurred in two phases (1988 – 1991 and 1991 – 1994); we combined and analyzed data from both phases. After screening of 39,695 individuals for participation in the study, 33,994 eligible adults who agreed to participate were initially interviewed in their households for sociodemographic and medical history information. Participants were then invited to a Mobile Examination Center (MEC) for the collection of

biological samples, physical examinations, and physiological tests. Of the 33,994 interviewed adults, 30,818 subjects completed an examination at a MEC. Of these 30,818 subjects that completed a MEC visit, a random half-sample of adults aged 20–59 (n = 5,662) years completed central nervous system (CNS) evaluation tests, including our measures of cognitive function which are described in detail below. 1,005 of these subjects did not have complete information on all measurements necessary to generate a physiologic dysfunction score, primarily due to missing information on serum biomarkers (mostly a function of the NHANES sampling design). Of the remaining 4,657 subjects, 146 exclusions were made due to missing covariate data or for unclear responses to covariate variable questions (e.g. "Don't Know"). Ultimately, we examined data from 4,511 subjects with complete information on physiologic measures, cognitive function, and covariates.

Measures of Cognitive Function

The central nervous system (CNS) function evaluation component of NHANES III utilized the Neurobehavioral Evaluation System 2 (NES2), a validated, computerized cognitive function test battery(34). The NES2 consisted of three test components: (1) The simple reaction time test (SRTT); (2) the symbol digit substitution test (SDST); and (3) the serial digit learning test (SDLT). Extensive details on the methods and background of this test battery and its implementation in NHANES III are published elsewhere(35).

SRTT is a measure of visuomotor speed that consists of measuring the latency that occurs between the display of an object on a computer screen and the subject pressing a button(34). Each subject completed 50 consecutive trials of the SRTT. Mean latency (milliseconds) of these 50 trials served as an outcome measure in this analysis.

SDST is a measure of symbol coding speed, tapping into domains of perceptual-motor speed and coding ability. Subjects are presented with pairings of a single digit ('1' through '9') to each of nine different visual symbols in a grid format. The same symbols are shown elsewhere on the screen in a randomized order. The subject is asked to assign the proper digits to the corresponding symbols, using the original grid as a guide. Four trials of the SDST were conducted per subject with the computer recording the number of errors (nine possible) and the length of time needed for completion (seconds) for each trial. For each trial, a summary measure was generated by dividing the length of time needed to complete the nine pairings by the number of correct pairings. The overall SDST summary measure provided by the NHANES and used in this analysis consists of averaging the two trials (out of four) with the lowest scores.

SDLT measures working memory and learning. Subjects were shown a series of eight digits on the computer screen, each shown one at a time, with each new digit appearing after a brief delay. After all digits were shown, the subject was asked to reproduce the series on the keyboard. If an incorrect pattern was input, the screen would produce the same series of digits and the subject would be given another chance to input the digits. Each subject repeated this until two, consecutive trials were successfully completed or eight trials were completed with errors. An overall summary score was calculated based on how many trials needed to be completed and how many errors were observed in each trial. This total score ranged from 0 to 16, with '0' corresponding to fewer trials and greater success and '16' corresponding to more trials and less success.

Measure of Physiologic Dysfunction

A measure of physiologic dysfunction was created from biomarkers and physical measurements including: systolic blood pressure (SBP), diastolic blood pressure (DBP), waist to hip ratio (WHR), glycohemoglobin (GH), albumin (ALB), creatinine clearance

(CC), total cholesterol (TC), triglycerides (TG), white blood cell count (WBC), and resting heart rate (HR). CC was estimated through the use of the Cockcroft and Gault formula(36). Venipuncture samples of 100+ mL and spot urine specimens by the clean-catch technique into sterile 250-mL polyethylene containers were collected during the MEC visit. Frozen samples were sent to CDC for laboratory analysis. The Bio-Rad DIAMAT (Iris Technologies, Olathe, KS, USA) glycosylated hemoglobin analyzer system, using ion exchange high-performance liquid chromatography (HPLC), employed to measure glycohemoglobin from whole blood. The Boehringer Mannheim Diagnostics (Indianapolis, IN, USA) albumin system was used to quantify albumin. Urinary creatinine was measured with a Beckman Synchron AS/ASTRA clinical analyzer (Beckman Instruments, Brea, CA, USA). A Hitachi Model 737 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA) was used to measure both total cholesterol and triglycerides. White blood cell counts were determined through the Coulter S-PLUS JR (Beckman Coulter, Brea, CA, USA). Additional details on laboratory procedures are available elsewhere(37).

These health measures encompass cardiovascular, liver, and kidney organ systems. Multiple methods of computing such an index have been used in the literature; we calculate two versions of a simple scoring procedure, following prior work on allostatic load (Table 1)(20, 38, 39). Our scoring method assumes that each component equally contributes to one's physiologic dysfunction score and does not explicitly consider endocrine hormones such as cortisol, which were not available in NHANES III.

The first version utilized clinically-relevant cutoffs for each biomarker(38). A composite physiologic dysfunction score was assigned to each subject as a count of how many markers an individual exceeded the clinically significant level. For eight of the markers the count was incremented by one if an individual's value for a particular marker was greater than its clinical cutpoint. For the two remaining markers, for which very low values are clinically meaningful (ALB and CC), the count was incremented by one if the individual's value was less than a low-end clinical threshold. This procedure yields a maximum count of 10. We know of no clinically relevant threshold for WBC, so the 75th percentile value for MEC sample subjects was used.

To verify the robustness of potential associations, we created a second physiologic dysfunction score based on percentiles, as was done in previous NHANES-based analyses(16). We calculated unweighted quartiles from the distribution of each biomarker derived from the 13,580 subjects that completed the MEC portion of NHANES III. Subsequently, a composite physiologic dysfunction score was assigned to each of our 4,511 study subjects based on whether individuals exceeded the 75th percentile of each marker or fell below the 25th percentile, as described. For both versions of the scoring procedure, WBC was chosen as an immunologic marker over C-reactive protein (CRP) due to a large sample size reduction that would have occurred had we used CRP (resulting n= 3,100). To determine whether this would affect our results, we compared biological dysfunction scores generated with both WBC and CRP (where available) and calculated a Spearman rank correlation to assess comparability. The resulting ranking of dysfunction scores, based on clinical cutoffs, was nearly identical ($\rho = 0.96$).

Statistical Analysis

We conducted descriptive analyses to examine how covariate values varied across cognitive test outcomes, using weighted means and spearman rank correlations. We conducted multiple linear regression with SRTT, SDST and SDLT scores as dependent variables and physiologic dysfunction scores (based on clinically-relevant and percentile-based cutoffs) as exposure variables. SRTT, SDST, and SDLT scores were analyzed as continuous measures, though based on an assessment of residuals the SRTT and SDST scores were log-

transformed to achieve approximate normality for regression analysis. In addition to analyzing continuous, overall physiologic dysfunction scores, we evaluated the continuous, individual components of our scores to determine which components might be the primary contributors to an association between the overall physiologic dysfunction score and cognition. In order to determine whether the exclusion of 1,151 subjects with missing physiologic and covariate measures would bias results, we compared exclusion status with the three cognitive outcome measures. Exclusion status was not associated with any of the three tests of cognition, suggesting that the exclusion of 1,151 subjects did not materially bias results.

We included a range of covariates in the regression analysis based on their potential associations with either biological dysfunction scores or test performance, and through examination of covariates used in prior studies that utilized the NES2(35, 40). The covariates we selected are thought to be broad representations of the constructs of socioeconomic status, as well as vascular health, energy and fitness. All of these factors have been shown to be associated with cognition in nationally-representative data(35, 40) and should capture the elements of other socioeconomic status, vascular health, and energy-related covariates that were not considered here. Factors encompassing overall health were not included to avoid overadjustment.

We included the following demographic and socioeconomic variables as additional covariates for regression analysis: sex, age (continuous), years of education completed (continuous), reported ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican-American, Other), self-rated familiarity with computers ("A lot," "Some," or "None"), alcohol use in the previous three hours (No drinks, or 1+), test language (English or non-English), self-reported energy level (feeling exhausted/tired or not), ever experiencing a stroke (Yes or No, self-reported), and a question regarding how the subject perceived their state of physical activity compared with their peers ("More active," "About the same," "Less Active"). We also controlled for a ratio of household income to poverty threshold (IPR; the ratio of reported household income over the federal poverty level given number of people in the household)(41). However, this covariate did not materially affect the findings and IPR values were missing for 9.8% of participants. Therefore, to maximize the sample size while still accounting for confounding by socioeconomic status, we report results controlling for ethnicity and education, which were not limited by item non-response to the same degree as IPR.

For each of the three cognitive endpoints, a series of three nested models were analyzed to identify potentially important confounders or mediators: (1) a initial multiple linear regression model, regressing each cognitive test score on overall dysfunction and individual components, adjusting for sex and age, (2) a larger model adjusting for sociodemographic variables (sex, age, years of education, and ethnicity), (3) and a final model adjusting for the sociodemographic variables and additionally self-reported familiarity with computers, recent alcohol use, test language, self-reported energy level, history of stroke, and perception of physical activity level. Each of these multiple linear regressions were repeated using the alternative, percentile-based, version of our physiologic dysfunction score.

Multiple linear regression assumptions were graphically verified for every model: for each regression model a histogram of residuals was created to verify normality, and a plot of continuous dysfunction scores against model residuals was created to observe potential heteroscedasticity. We verified the assumption of a linear relationship between physiologic dysfunction scores and cognitive test outcomes (linear for SDLT, and linear for log SDTT and log SDST) by generating probability-weighted, kernel-smoothed scatterplots, using both unadjusted and fully adjusted models with the "survey" package of R 2.11.1 (R Foundation

for Statistical Computing, Vienna, Austria). In all other analyses, we accounted for the complex survey design used in NHANES III by employing the SURVEYMEANS, SURVEYREG, procedures of SAS 9.2 (SAS Institute, Inc. Cary, North Carolina, USA). The CNS sub-sample probability weights were used in all analyses.

RESULTS

Within this sample of 4,511 subjects, the distribution of cumulative physiologic dysfunction scores ranged from zero to nine with a weighted median value of 1 (lower quartile = 1, upper quartile = 2) and a weighted mean value of 1.49. Table 2 displays weighted frequencies of covariates for the study population as well as weighted mean cognitive test values within levels of each covariate. Study participants had a median age of 36 years, and were about equally distributed by sex. Approximately 77% of participants (in weighted sample) described themselves as non-Hispanic White.

Table 3 displays results from fully-adjusted multiple regression models predicting each cognitive domain score as a function of the physiological dysfunction overall score (derived from clinical cutoffs) as well as the score's individual components. Considering the log SRTT (visuomotor speed) outcome, only the unadjusted model provided evidence of a relationship between dysfunction scores (data not shown). Although higher biological dysfunction scores were associated with delayed symbol coding speed for the log SDST (symbol coding speed) in the unadjusted and SES-adjusted models (data not shown), this association was not significant in our full model that also controls for cognitive test conditions (Table 3). On the other hand, the continuous physiologic dysfunction variable predicted increased number of errors in the SDLT (the working memory and learning test) scores (coefficient = 0.207, 95% CI = (0.066, 0.348)), an observation which was not greatly affected by controlling for confounders. While the overall dysfunction score was significantly associated with the working memory test, no individual component measure of the dysfunction score was associated with working memory errors. Regression models using the physiologic dysfunction score constructed from percentile-based cutoffs corroborated these results; in the full model, only the SDLT test results were associated with the continuous dysfunction index (coefficient = 0.126, 95% CI = (0.014, 0.238)). This dose-response relationship between physiologic dysfunction and SDLT scores is illustrated in Figure 1.

DISCUSSION

We observed a robust cross-sectional association between increased cumulative physiological dysfunction and deficits in short-term, working memory but not with perceptual and visuomotor skills. Interestingly, we found that no individual component of physiologic dysfunction was related working memory deficits, after adjusting for potentially confounding covariates. This suggests that aggregate physiologic dysfunction may be a more important measure than dysfunction in any given individual factor.

The conceptual model of allostatic load, describing the damaging effects of allostasis, provides a framework for explaining the variation we observed in working memory in relation to physiologic dysfunction(12, 14). Continual allostasis is thought to affect multiple organ systems, influencing levels of immune system effectors, cardiovascular function, and metabolism(12, 14, 15). A recent analysis demonstrated that the endocrine disruption that is thought to be the primary signal of allostatic load is captured by multiple domains of physiologic dysfunction, including the cardiovascular, metabolic, and immune systems(13). Thus, multisystem physiologic dysfunction may be indicative of HPA-axis dysregulation and hypercortisolism(14, 15). Indeed, cortisol release is thought to affect particular brain

regions such as the PFC and hippocampus, which are responsible for memory, executive function, spatial skills(15, 42, 43). In summary, total physiologic dysfunction and aberrant HPA-axis activity are thought to occur through continual allostasis, which in turn may affect multiple domains of cognitive function.

It is believed that dopaminergic activity within the PFC is crucial in the development and function of working memory(44). The release of glucocorticoids such as cortisol has been shown to impair working memory in rats via inhibition of dopaminergic activity in the HPA-axis(44). Seeman et al. noted that elevated urinary cortisol release is associated with poorer memory function among women(45). Thus, although we cannot evaluate this specific pathway in our study, our analyses focusing on other, available physiological components within the allostatic load framework are consistent with the possibility that the memory deficits we observed might potentially be due to HPA-axis dysfunction and the resultant elevated glucocorticoid levels affecting PFC activity. With regard to our negative findings for other domains of cognition, it is possible that visuomotor measurements were unassociated with physiologic dysfunction due to the involvement of brain structures such as the inferior parietal lobule, which are less associated with the HPA-axis cascade(46, 47).

Our primary finding supports the prior research conducted on this topic by Seeman et al. (20). In their prospective sample, they demonstrated how an allostatic load score could predict decline in cognitive function among a sample of 765 high functioning elderly men and women(20). Their study constructed an allostatic load score from some of the physiologic measurements used in the present analysis as well as serum dehydroepiandrosterone sulfate, urinary cortisol, norepinephrine, and epinephrine levels. Statistically significant, inverse correlations were observed between allostatic load scores and memory, spatial ability, and abstract reasoning, after adjustment for confounders.

Several limitations of the present analysis must be considered when interpreting the findings. First, as we used a cross-sectional sample, we cannot infer causal relationships with this analysis. In addition, the biological processes discussed in this analysis are highly dynamic and with this cross-sectional design we are unable to fully capture these dynamic associations. Unfortunately, currently available nationally-representative longitudinal data, such as the NHANES I Epidemiologic Follow-up Study(48), do not contain information on relevant outcomes and covariates to shed further light on this issue. Second, concerns could be raised regarding the use of an aggregate physiologic dysfunction score and the arbitrary nature of cutpoints. While particular approaches to the operationalization of allostatic load may vary across studies, it has been suggested that measures driven by the allostatic load framework should employ component measures from as many systems of the body as possible(18). We believe that our measure of physiologic dysfunction, which is similar to measures used elsewhere(17, 49), meets this criterion as it includes a wide-ranging combination of component measures. Third, in order to satisfy the assumptions for our linear regression models we log-transformed two of our three dependent variables. While this approach is common practice, other approaches may yield different findings (e.g., alternative transformations, or categorizing the dependent variable and using ordered or multinomial response models) as they also embody different assumptions about the forms of the relationships of interest. Fourth, the data were collected about two decades ago, which may affect generalizability of the findings. However, both the exposure and outcome measures represent biological processes, and we do not believe or expect both to systematically change over a few decades and thus significantly influence the inferences we draw from the analysis. Finally, and perhaps most significantly, the third NHANES did not collect data on HPA-axis functional status measures. Adding this information would bring our measure closer to a formulation of allostatic load used in prior work, and would provide a more solid foundation for implicating allostatic load in the etiology of cognitive decline.

Thus, although we cannot evaluate this specific pathway (HPA-axis function) in our study, our findings based on other, available physiological components within the allostatic load framework are compatible with the possibility that the memory deficits we observed may potentially be due to HPA-axis dysfunction and the resultant elevated glucocorticoid levels affecting PFC activity.

Nevertheless, our analysis has several strengths. This is one of the few analyses to examine how cumulative physiologic dysfunction, guided by the allostatic load model, relates to specific dimensions of cognitive performance, rather than global measures of cognitive performance. A particular strength of this analysis is the study population; it is a nationally-representative sample and the largest population in which this topic has been investigated. We also use a comprehensive battery of physiological measures, obtaining similar results with two different biological dysfunction score algorithms. This suggests that the arbitrary nature of our cutoffs has little impact on ranking participants according to physiologic dysfunction scores. Finally, we employed the validated and reliable NES2 cognitive battery(34, 50), which has been extensively used in prior studies(35, 40, 51–54). It appears unlikely that physiologic dysfunction was unrelated to SRTT and SDST test results due to poor measurement of these cognitive domains, because a prior analysis noted that these tests were sensitive to cognitive domains performance differences between controls and patients with neurological disorders(50). Although the method in which cognitive performance scores are modeled (e.g., untransformed vs. log-transformed, continuous vs. categorical) may affect the ultimate results of statistical analysis, in this analysis we employed the standard scoring method adopted by the NHANES III and an analytic approach similar to those of prior analyses(53).

The finding that overall, physiological dysfunction is linked with deficits in working memory has public health ramifications. We observed this association among a population that exclusively contains early-to-mid-life adults. Future longitudinal studies are needed to clarify the extent to which HPA-axis dysfunction drives this association and explore the persistency of this association into later life. We suggest that such studies should incorporate physiologic data, neuroendocrine parameters, and a wide range of specific cognitive domains. If our findings are confirmed in these more rigorous studies, it may be possible to earlier identify populations who may be at increased risk of accelerated cognitive decline based on their allostatic load profile.

Acknowledgments

Acronyms

BMI	body mass index
HPA	hypothalamic-pituitary-adrenal
PFC	pre-frontal cortex
NHANES	National Health and Nutrition Examination Survey
MEC	Mobile Examination Center
CNS	central nervous system

NES2	Neurobehavioral Evaluation System 2
SRTT	simple reaction time test
SDST	symbol digit substitution test
SDLT	serial digit learning test
SBP	systolic blood pressure
DBP	diastolic blood pressure
WHR	waist to hip ratio
GH	glycohemoglobin
ALB	albumin
CC	creatinine clearance
TC	total cholesterol
TG	triglycerides
WBC	white blood cell count
HR	resting heart rate
CRP	C-reactive protein

REFERENCES

1. Buchman AS, Tanne D, Boyle PA, Shah RC, Leurgans SE, Bennett DA. Kidney function is associated with the rate of cognitive decline in the elderly. Neurology. 2009; 73:920–927. [PubMed: 19657107]

2. del Ser T, Barba R, Morin MM, Domingo J, Cemillan C, Pondal M, Vivancos J. Evolution of cognitive impairment after stroke and risk factors for delayed progression. Stroke. 2005; 36:2670–2675. [PubMed: 16254227]

3. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, Culliford D, Perry VH. Systemic inflammation and disease progression in Alzheimer disease. Neurology. 2009; 73:768–774. [PubMed: 19738171]

4. Muller M, Grobbee DE, Aleman A, Bots M, van der Schouw YT. Cardiovascular disease and cognitive performance in middle-aged and elderly men. Atherosclerosis. 2007; 190:143–149. [PubMed: 16488420]

5. Roman G. Vascular dementia: a historical background. Int Psychogeriatr. 2003; 15(Suppl 1):11–13. [PubMed: 16191211]

6. Rose KM, Couper D, Eigenbrodt ML, Mosley TH, Sharrett AR, Gottesman RF. Orthostatic Hypotension and Cognitive Function: The Atherosclerosis Risk in Communities Study. Neuroepidemiology. 2009; 34:1–7. [PubMed: 19893322]

7. Wang F, Zhang L, Liu L, Wang H. Level of kidney function correlates with cognitive decline. Am J Nephrol. 2010; 32:117–121. [PubMed: 20714128]

8. Weissenborn K, Bokemeyer M, Krause J, Ennen J, Ahl B. Neurological and neuropsychiatric syndromes associated with liver disease. AIDS. 2005; 19(Suppl 3):S93–S98. [PubMed: 16251835]

9. Christman AL, Matsushita K, Gottesman RF, Mosley T, Alonso A, Coresh J, Hill-Briggs F, Sharrett AR, Selvin E. Glycated haemoglobin and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study. Diabetologia. 2011; 54:1645–1652. [PubMed: 21360189]

10. Kerwin DR, Zhang Y, Kotchen JM, Espeland MA, Van Horn L, McTigue KM, Robinson JG, Powell L, Kooperberg C, Coker LH, Hoffmann R. The cross-sectional relationship between body mass index, waist-hip ratio, and cognitive performance in postmenopausal women enrolled in the Women's Health Initiative. J Am Geriatr Soc. 2010; 58:1427–1432. [PubMed: 20646100]

11. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001; 285:2486–2497. [PubMed: 11368702]

12. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med. 1993; 153:2093–2101. [PubMed: 8379800]

13. Seeman T, Gruenewald T, Karlamangla A, Sidney S, Liu K, McEwen B, Schwartz J. Modeling multisystem biological risk in young adults: The Coronary Artery Risk Development in Young Adults Study. Am J Hum Biol. 2010; 22:463–472. [PubMed: 20039257]

14. McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. Ann N Y Acad Sci. 1999; 896:30–47. [PubMed: 10681886]

15. McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci. 1998; 840:33–44. [PubMed: 9629234]

16. Geronimus AT, Hicken M, Keene D, Bound J. 'Weathering' and age patterns of allostatic load scores among blacks and whites in the United States. Am J Public Health. 2006; 96:826–833. [PubMed: 16380565]

17. Crimmins EM, Johnston M, Hayward M, Seeman T. Age differences in allostatic load: an index of physiological dysregulation. Exp Gerontol. 2003; 38:731–734. [PubMed: 12855278]

18. Dowd JB, Simanek AM, Aiello AE. Socio-economic status, cortisol and allostatic load: a review of the literature. Int J Epidemiol. 2009; 38:1297–1309. [PubMed: 19720725]

19. Juster RP, Marin MF, Sindi S, Nair NP, Ng YK, Pruessner JC, Lupien SJ. Allostatic load associations to acute, 3-year and 6-year prospective depressive symptoms in healthy older adults. Physiol Behav. 2011; 104:360–364. [PubMed: 21352837]

20. Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS. Price of adaptation--allostatic load and its health consequences. Arch Intern Med. 1997; 157:2259–2268. [PubMed: 9343003]

21. Evans GW, Schamberg MA. Childhood poverty, chronic stress, and adult working memory. Proc Natl Acad Sci U S A. 2009; 106:6545–6549. [PubMed: 19332779]

22. Wright CE, Kunz-Ebrecht SR, Iliffe S, Foese O, Steptoe A. Physiological correlates of cognitive functioning in an elderly population. Psychoneuroendocrinology. 2005; 30:826–838. [PubMed: 15975730]

23. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev. 2009

24. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev. 2007; 87:873–904. [PubMed: 17615391]

25. Yuen EY, Liu W, Karatsoreos IN, Feng J, McEwen BS, Yan Z. Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. Proc Natl Acad Sci U S A. 2009; 106:14075–14079. [PubMed: 19666502]

26. Fuster JM. Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. J Neurophysiol. 1973; 36:61–78. [PubMed: 4196203]

27. McEwen BS. Stress and hippocampal plasticity. Annu Rev Neurosci. 1999; 22:105–122. [PubMed: 10202533]

28. Nielsen L, Mather M. Emerging perspectives in social neuroscience and neuroeconomics of aging. Soc Cogn Affect Neurosci. 2011; 6:149–164. [PubMed: 21482573]

29. Richards M, Hatch SL. A Life Course Approach to the Development of Mental Skills. J Gerontol B Psychol Sci Soc Sci. 2011

30. Tucker-Drob EM. Global and domain-specific changes in cognition throughout adulthood. Dev Psychol. 2011; 47:331–343. [PubMed: 21244145]

31. Middleton LE, Barnes DE, Lui LY, Yaffe K. Physical activity over the life course and its association with cognitive performance and impairment in old age. J Am Geriatr Soc. 2010; 58:1322–1326. [PubMed: 20609030]

32. Alderson AL, Novack TA. Neurophysiological and clinical aspects of glucocorticoids and memory: a review. J Clin Exp Neuropsychol. 2002; 24:335–355. [PubMed: 11992216]

33. Centers for Disease Control and Prevention (CDC). National Health and Nutrition Examination Survey Protocol. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2009. National Center for Health Statistics (NCHS).

34. Baker EL, Letz RE, Fidler AT, Shalat S, Plantamura D, Lyndon M. A computer-based neurobehavioral evaluation system for occupational and environmental epidemiology: methodology and validation studies. Neurobehav Toxicol Teratol. 1985; 7:369–377. [PubMed: 4058646]

35. Krieg EF Jr, Chrislip DW, Letz RE, Otto DA, Crespo CJ, Brightwell WS, Ehrenberg RL. Neurobehavioral test performance in the third National Health and Nutrition Examination Survey. Neurotoxicol Teratol. 2001; 23:569–589. [PubMed: 11792526]

36. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16:31–41. [PubMed: 1244564]

37. Gunter, EW.; Lewis, BG.; Koncikowski, SM. Laboratory Procedures Used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. Atlanta, GA: U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; 1996.

38. Merkin SS, Basurto-Davila R, Karlamangla A, Bird CE, Lurie N, Escarce J, Seeman T. Neighborhoods and cumulative biological risk profiles by race/ethnicity in a national sample of U.S. adults: NHANES III. Ann Epidemiol. 2009; 19:194–201. [PubMed: 19217002]

39. Seplaki CL, Goldman N, Weinstein M, Lin YH. Measurement of cumulative physiological dysregulation in an older population. Demography. 2006; 43:165–183. [PubMed: 16579213]

40. Krieg EF Jr, Chrislip DW, Crespo CJ, Brightwell WS, Ehrenberg RL, Otto DA. The relationship between blood lead levels and neurobehavioral test performance in NHANES III and related occupational studies. Public Health Rep. 2005; 120:240–251. [PubMed: 16134563]

41. "Poverty: Definitions". United States Census Bureau. [05/31/2011]; Available from: http://www.census.gov/hhes/www/poverty/methods/definitions.html#ratio%20of%20income%20to%20poverty.

42. McLaughlin KJ, Gomez JL, Baran SE, Conrad CD. The effects of chronic stress on hippocampal morphology and function: an evaluation of chronic restraint paradigms. Brain Res. 2007; 1161:56–64. [PubMed: 17603026]

43. Stuss, DT.; Knight, RT. Principles of frontal lobe function. Oxford ; New York: Oxford University Press; 2002.

44. Mizoguchi K, Ishige A, Takeda S, Aburada M, Tabira T. Endogenous glucocorticoids are essential for maintaining prefrontal cortical cognitive function. J Neurosci. 2004; 24:5492–5499. [PubMed: 15201321]

45. Seeman TE, McEwen BS, Singer BH, Albert MS, Rowe JW. Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. J Clin Endocrinol Metab. 1997; 82:2458–2465. [PubMed: 9253318]

46. Goldberg ME, Bisley JW, Powell KD, Gottlieb J. Saccades, salience and attention: the role of the lateral intraparietal area in visual behavior. Prog Brain Res. 2006; 155:157–175. [PubMed: 17027387]

47. Schnell K, Heekeren K, Daumann J, Schnell T, Schnitker R, Moller-Hartmann W, Gouzoulis-Mayfrank E. Correlation of passivity symptoms and dysfunctional visuomotor action monitoring in psychosis. Brain. 2008; 131:2783–2797. [PubMed: 18713781]

48. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). NHANES I Epidemiologic Followup Study (NHEFS). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; [04/01/2011]; Available from: http://www.cdc.gov/nchs/nhanes/nhefs/nhefs.htm#survey

49. Bird CE, Seeman T, Escarce JJ, Basurto-Davila R, Finch BK, Dubowitz T, Heron M, Hale L, Merkin SS, Weden M, Lurie N. Neighbourhood socioeconomic status and biological 'wear and tear' in a nationally representative sample of US adults. J Epidemiol Community Health. 2010; 64:860–865. [PubMed: 19759056]

50. White RF, Diamond R, Krengel M, Lindem K, Feldman RG, Letz R, Eisen E, Wegman D. Validation of the NES2 in patients with neurologic disorders. Neurotoxicol Teratol. 1996; 18:441–448. [PubMed: 8866536]

51. Hailpern SM, Melamed ML, Cohen HW, Hostetter TH. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National Health and Nutrition Examination Survey (NHANES III). J Am Soc Nephrol. 2007; 18:2205–2213. [PubMed: 17554148]

52. Pavlik VN, Hyman DJ, Doody R. Cardiovascular risk factors and cognitive function in adults 30–59 years of age (NHANES III). Neuroepidemiology. 2005; 24:42–50. [PubMed: 15459509]

53. Suhr JA, Stewart JC, France CR. The relationship between blood pressure and cognitive performance in the Third National Health and Nutrition Examination Survey (NHANES III). Psychosom Med. 2004; 66:291–297. [PubMed: 15184686]

54. Gouvier WD, Pinkston JB, Lovejoy JC, Smith SR, Bray GA, Santa Maria MP, Hammer JH, Hilsabeck RC, Smiroldo B, Bentz B, Browndyke J. Neuropsychological and emotional changes during simulated microgravity: effects of triiodothyronine alendronate, and testosterone. Arch Clin Neuropsychol. 2004; 19:153–163. [PubMed: 15010082]

55. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998; 15:539–553. [PubMed: 9686693]

56. Golden S, Boulware LE, Berkenblit G, Brancati F, Chander G, Marinopoulos S, Paasche-Orlow M, Powe N, Rami T. Use of glycated hemoglobin and microalbuminuria in the monitoring of diabetes mellitus. Evid Rep Technol Assess (Summ). 2003:1–6. [PubMed: 15040142]

57. Visser M, Kritchevsky SB, Newman AB, Goodpaster BH, Tylavsky FA, Nevitt MC, Harris TB. Lower serum albumin concentration and change in muscle mass: the Health, Aging and Body Composition Study. Am J Clin Nutr. 2005; 82:531–537. [PubMed: 16155264]

58. Maithel SK, Pomposelli FB, Williams M, Sheahan MG, Scovell SD, Campbell DR, LoGerfo FW, Hamdan AD. Creatinine clearance but not serum creatinine alone predicts long-term postoperative survival after lower extremity revascularization. Am J Nephrol. 2006; 26:612–620. [PubMed: 17183190]

59. Seccareccia F, Pannozzo F, Dima F, Minoprio A, Menditto A, Lo Noce C, Giampaoli S. Heart rate as a predictor of mortality: the MATISS project. Am J Public Health. 2001; 91:1258–1263. [PubMed: 11499115]
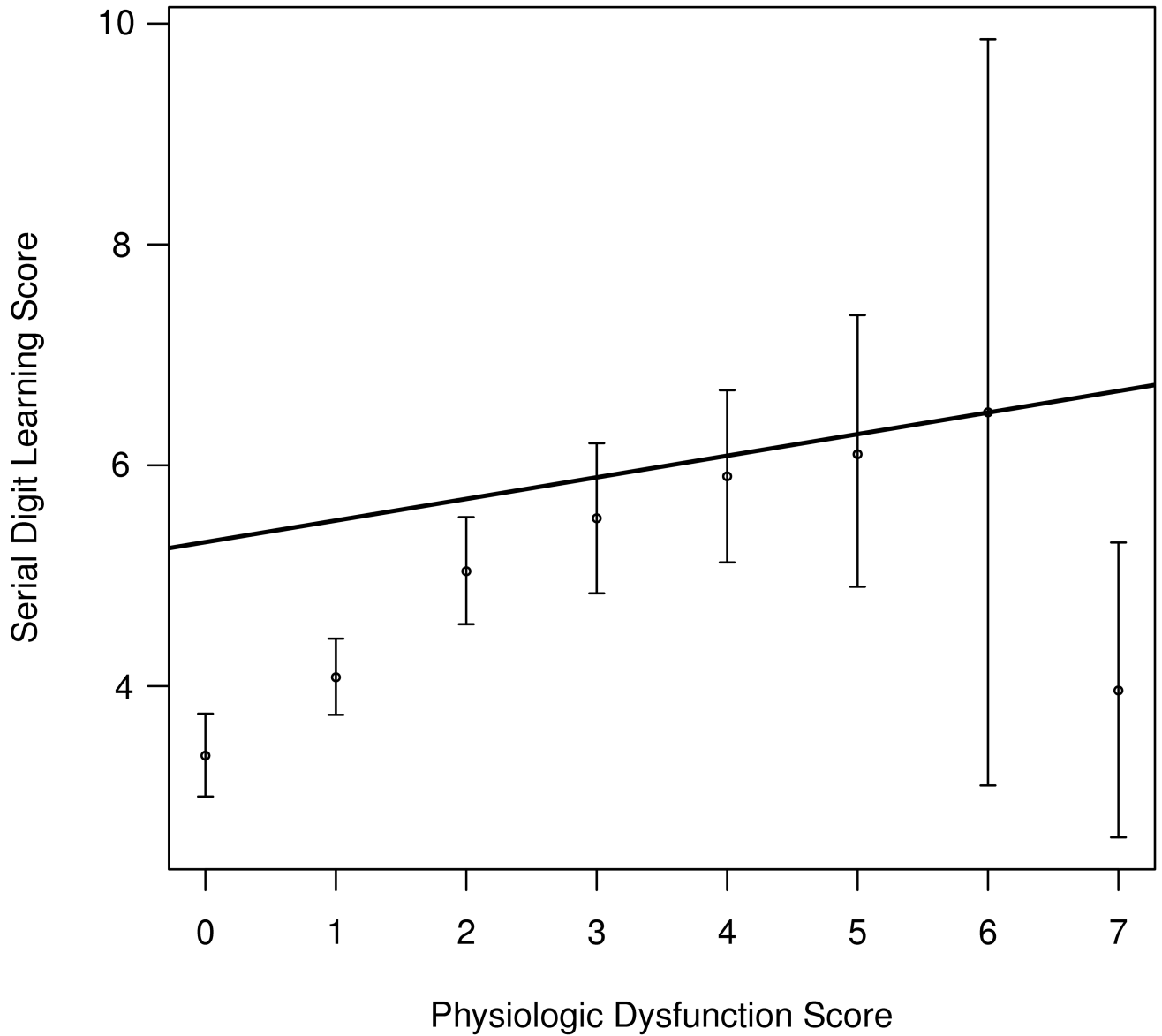
Figure 1.
Crude means of Serial Digit Learning Test scores across levels of physiologic dysfunction. Error bars indicate 95% confidence intervals of the mean. The regression line from fully-adjusted model (coefficient = 0.207) is included. All calculations accounted for the complex survey design.

Table 1

Percentile and clinically-relevant based cutoffs used to construct total physiologic dysfunction composite score.

Components of Physiologic Dysfunction Score	Clinically-relevant Algorithm(38) (N above, below cutoff)		Percentile-based Algorithm
Systolic blood pressure (SBP)(11)	> 140 mmHg	(362; 4149)	> 130 mmHg
Diastolic blood pressure (DBP)(11)	> 90 mmHg	(290; 4221)	> 78 mmHg
Waist to hip ratio (WHR)(55)	> 0.9 (men) > 0.8 (women)	(1456; 632) (1257; 1166)	> 0.98
Glycohemoglobin (GH)(56)	> 6.4%	(206; 4305)	> 5.6%
Albumin (ALB)(57)	< 3.8 g/dL	(513; 3998)	< 3.9 g/dL
Creatinine clearance (CC)(58)	< 60 mL/min	(146; 4365)	< 67 mL/min
Total cholesterol (TC)(11)	> 240 mg/dL	(664; 3847)	> 220 mg/dL
Triglycerides (TG)(11)	> 200 mg/dL	(682; 3829)	> 154 mg/dL
White Blood Cell Count (WBC)[1]	$> 8.4 \times 10^9$ cells /L	(1102; 3409)	$> 8.4 \times 10^9$ cells /L
Resting heart rate (HR)(59)	> 90 bpm	(452; 4059)	> 84 bpm

[1]Clinically-relevant cutoff could not be identified

SBP = systolic blood pressure; DBP = diastolic blood pressure; WHR = waist to hip ratio; GH = glycohemoglobin; ALB = albumin; CC = creatinine clearance; TC = total cholesterol; TG = triglycerides; WBC = white blood cell count; HR = resting heart rate

Table 2

Final sample descriptive statistics and weighted mean scores of simple reaction time test (SRTT), symbol digit substitution test (SDST), and serial digit learning test (SDLT).

Covariates	Number of Observations	Unweighted Percentage (Weighted Percentage)	Tests of Cognitive Function		
			SRTT[1] (msecs)	SDST[1] (secs/correct items)	SDLT[1] (0–16 score)
Sex					
Men	2088	46.3% (49.9%)	225.9	2.74	4.37
Women	2423	53.7% (50.1%)	240.4	2.60	4.47
Age (Spearman correlation)			0.07	0.38	0.18
Years of Education (Spearman correlation)			−0.23	−0.53	−0.46
Ethnicity					
N-H White	1615	35.8% (77.0%)	229.7	2.55	3.73
N-H Black	1366	30.3% (10.6%)	247.6	3.02	6.06
Mexican American	1361	30.2% (5.6%)	247.7	3.19	7.91
Other	169	3.7% (6.8%)	238.7	3.01	7.05
Familiarity With Computers					
"None"	1879	41.7% (29.4%)	244.3	3.24	6.98
"Some"	1989	44.1% (52.6%)	229.3	2.51	3.64
"A lot"	643	14.3% (18.0%)	226.5	2.22	2.66
Recent Alcohol Use					
0 drinks	4459	98.8% (31.9%)	233.1	2.67	4.41
1 + drinks	52	1.2% (68.1%)	244.5	3.45	7.30
Test Language					
English	3914	86.8% (96.0%)	231.9	2.62	4.16
Non-English	597	13.2% (4.0%)	263.4	3.91	10.97
Energy Level					
Average or better	3326	73.7% (72.9%)	230.8	2.65	4.36
Tired or exhausted	1185	26.3% (27.1%)	239.6	2.72	4.56
Stroke					
Yes	29	0.6% (0.6%)	254.5	3.26	7.63

Covariates

Tests of Cognitive Function

	Number of Observations	Unweighted Percentage (Weighted Percentage)	SRTT[1] (msecs)	SDST[1] (secs/correct items)	SDLT[1] (0–16 score)
No	4482	99.4% (99.4%)	233.1	2.67	4.40
Amount of Exercise Relative to Peers					
More active	1303	28.9% (31.1%)	226.6	2.68	4.01
Equally active	2169	48.1% (46.4%)	234.4	2.69	4.64
Less Active	1039	23.0% (22.5%)	239.8	2.62	4.54

[1]Calculated with CNS sub-sample weights

SRTT = simple reaction time test; SDST = symbol digit substitution test; SDLT = serial digit learning test; N-H White = Non-Hispanic White; N-H Black = Non-Hispanic Black

Table 3

Fully-adjusted multiple linear regression model coefficients predicting log simple reaction time (SRTT), log symbol digit substitution test (SDST), and serial digit learning test (SDLT).[1,2,3]

Physiologic Dysfunction Components and Overall Score[6]	Log(SRTT) Coefficient (95% CI)[4,5]	Log(SDST) Coefficient (95% CI)[4,5]	SDLT Coefficient (95% CI)[5]
SBP	−0.0002 (−0.0008, 0.0003)	−0.00008 (−0.0007, 0.0005)	0 (−0.01, 0.011)
DBP	0.00006 (−0.0007, 0.0008)	0.0003 (−0.0004, 0.001)	0.007 (−0.008, 0.022)
WHR	0.000002 (−0.00001, 0.00001)	−0.000002 (−0.00001, 0.00001)	0.00005 (−0.0001, 0.0002)
GH	0.007 (−0.001, 0.015)	0.01 (−0.002, 0.03)	0.08 (−0.146, 0.307)
ALB	**−0.045 (−0.071, −0.018)**	−0.018 (−0.04, 0.003)	−0.236 (−0.896, 0.425)
CC	0.0003 (−0.00002, 0.0007)	0.00002 (−0.0003, 0.0004)	0.006 (−0.001, 0.013)
TC	−0.0001 (−0.0003, 0.00004)	−0.0001 (−0.0003, 0.0001)	0.002 (−0.002, 0.006)
TG	0.00002 (−0.00002, 0.00007)	0.00002 (−0.00003, 0.00007)	0.002 (−0.0002, 0.004)
WBC	0.001 (−0.002, 0.004)	0.002 (−0.002, 0.005)	0.048 (−0.021, 0.116)
HR	0.00009 (−0.0006, 0.0007)	0.0002 (−0.0004, 0.0008)	0.006 (−0.01, 0.021)
Overall Score	0.002 (−0.003, 0.007)	0.007 (0, 0.013)	**0.207 (0.066, 0.348)**

[1] Calculated with CNS sub-sample weights

[2] bold indicates two-sided significance of coefficients at 5% level

[3] Adjusted covariates include: sociodemographic model covariates + familiarity with computers, recent alcohol use, test language, energy level, self-reported history of stroke, and perceived average physical activity.

[4] Test scores are log transformed

[5] Calculated using clinical cutoffs

SRTT = simple reaction time test; SDST = symbol digit substitution test; SDLT = serial digit learning test; SBP = systolic blood pressure; DBP = diastolic blood pressure; WHR = waist to hip ratio; GH = glycohemoglobin; ALB = albumin; CC = creatinine clearance; TC = total cholesterol; TG = triglycerides; WBC = white blood cell count; HR = resting heart rate