# The Relationship between Stress, Physical Activity and Cognitive Decline with Age

by

Rebecca Vendittelli

B.Sc. (Hons.), York University, 2014

A Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of

MASTER OF SCIENCE

in the Department of Psychology

**Supervisory Committee**

The Relationship between Stress, Physical Activity and Cognitive Decline with Age

by

Rebecca Vendittelli

B.Sc. (Hons.), York University, 2014

**Supervisory Committee**

Dr. Andrea Piccinin (Department of Psychology)
Supervisor

Dr. Colette Smart (Department of Psychology)
Departmental Member

## Abstract

**Supervisory Committee**
Dr. Andrea Piccinin (Department of Psychology)
**Supervisor**

Dr. Colette Smart (Department of Psychology)
**Departmental Member**

Cognitive decline is often associated with increasing age. However, there is growing support that modifiable lifestyle factors such as exercise and stress influence outcomes. That is, physical activity (PA) seems to be protective, while stress engenders decline. Moreover, there is evidence to suggest that these variables interact such that being active positively moderates the negative effects of stress on cognitive decline. The present study examines the effects of both average PA and stress on cognitive decline (i.e., between-person effects), the coupled association between PA and cognition and stress and cognition (i.e., within-person, or occasion specific effects), and the possible interaction between PA and stress on cognitive outcomes. Coordinated analyses of The Memory and Aging Project (MAP; N = 1,853, mean age = 79) and Longitudinal Aging Study Amsterdam (LASA; N = 4,109, mean age = 68) were conducted. A series of multilevel models (MLM) were fit to the data, evaluating differences in baseline and linear change in perceptual speed, episodic memory, and MMSE scores in both data sets. Average PA was associated with the intercept of perceptual speed and episodic memory, and decline in all 3 outcomes in MAP only. There was a significant coupled association between PA and all cognitive outcomes in MAP, and with perceptual speed in LASA. Average stress was not associated with baseline scores or rates of change in any of the cognitive outcomes in either study. However, occasion specific stress was associated with perceptual speed and episodic memory in the unexpected direction in LASA. Lastly, there was a significant positive interaction

between occasion specific stress and occasion specific activity on MMSE and perceptual speed scores in LASA. That is, on occasions when participants reported more stress than usual, if they also reported more exercise than usual, they tended to score better on these outcomes. Findings support the beneficial effects of both average and occasion specific activity on cognitive abilities, however failed to demonstrate the adverse effects of stress, and only partially supported an interaction between activity and stress. Limitations and future directions are discussed.

Table of Contents

## List of Tables

## List of Figures

## Acknowledgments

I would first and foremost like to thank my supervisor, Dr. Andrea Piccinin, for the time and effort she dedicated to mentoring this project. Her continual support over that past two years has greatly contributed to my development as a researcher. I would also like to thank Andrey Koval, for his guidance and willingness to share his statistical knowledge. Andrey has gone above and beyond to assist in this project where his expertise was invaluable. Additionally, many thanks are in order to my committee members, Dr. Colette Smart, and Dr. Sandra Hundza, for their willingness to provide feedback and direction. Lastly, thank you to my cohort, it has been a pleasure to learn and develop alongside all of you over the course of this program.

I appreciate the support I have received for this project from the Canadian Institute of Health Research (CIHR) Master's Award and funding provided to me by the Integrative Analysis of Longitudinal Studies of Aging (IALSA) research network. Lastly, I am grateful to Dr. David Bennett, and the Memory and Aging Project research team at Rush University, and Dr. Huisman, Dr. Comijs, and the Longitudinal Aging Study Amsterdam research team at Vrije University, for conducting outstanding longitudinal studies and making research like the present investigation possible

## Introduction

As individuals age, the probability of developing non-normative cognitive impairment and dementia increases substantially. Severe decline in cognitive abilities is often debilitating, and those afflicted rely on others for their care. Thus, impairments not only affect the individual, but also significantly impact caregivers and increase health care burden. Approximately 564,000 Canadians are living with dementia and this number is expected to increase by 66% over the next 15 years (Alzheimer's Society of Canada, 2016), outweighing the available health care resources. However, there is a great deal of variation between individuals regarding cognitive status in their elderly years (Sofi et al., 2011). That is, while some develop severe cognitive impairments with increasing chronological age, others remain seemingly unscathed (Miller, Taler, Davidson, & Messier, 2012). Although modest declines in processing speed, episodic memory (as opposed to semantic), and executive functioning (EF) are considered part of the normal aging process (Harada, Natelson Love, & Triebel, 2013), it is becoming increasingly evident that severe cognitive decline is not an inevitable outcome caused by age. Rather, modifiable lifestyle factors significantly contribute to decline and dementia (Baumgart et al., 2015).

In attempts to avert a potential health care crisis, efforts to disentangle consistent differences between those who are considered to have successfully aged and those with relatively more severe cognitive impairments have been undertaken in recent years. Both physical activity (PA; Bherer, Erickson, & Liu-Ambrose, 2013) and stress (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007) have gained increasing support for their role in moderating cognitive functioning with increasing age, and have implications for proactive intervention.

**Physical Activity and Cognition**

Extensive evidence has accrued suggesting that individuals who are physically active incur great cognitive benefits. For example, studies with elderly participants demonstrate significant gains in cognition after exercise interventions (Colcombe et al., 2006; Kramer & Erickson, 2007). Colcombe and Kramer (2003) conducted a meta-analysis of literature from 1966 to 2001, examining aerobic fitness training and cognitive functioning in nondemented adults aged 55 to 80 years, reporting a moderate effect size (0.48), with the largest effect on EF processes such as planning, scheduling, working memory, multitasking and inhibition. The effects of PA on EF are echoed in more recent meta-analytic findings, demonstrating that compared to controls, intervention groups perform significantly better on EF tasks (Karr, Areshenkoff, Rast, & Garcia-Barrera, 2014). Additionally, the authors report that the benefits of PA were evident across both cognitively impaired and healthy subjects, underscoring the importance of exercise in older adults across varying levels of decline. Interestingly, relatively short interventions (e.g., 6 months) translate into brain changes such as increased activity in the frontal and parietal lobes during a focused attention task (Colcombe et al., 2004), and an increase in grey matter in the frontal and superior temporal lobes compared to controls (Kramer, Colcombe, Erickson, & Paige, 2006).

Although short-term experimental designs are exceptionally informative in demonstrating causal effects of PA on cognition, longitudinal analyses are necessary when examining how individuals change over time and the longevity of relationships between PA and cognition (Piccinin, Muniz, Sparks, & Bontempo, 2011). Longitudinal and prospective investigations often echo the beneficial effects of physical activity in protecting against cognitive decline and aging (e.g. see meta-analyses conducted by Blondell, Hammersley, Mather, & Veerman, 2014; Hamer

& Chida, 2009; Sofi et al., 2011). For example, low levels of self-reported PA have been associated with the development of Alzheimer's disease (AD) (Erickson, Weinstein, & Lopex, 2012; Podewils et al., 2005), and cognitive decline (Yaffe, Barnes, Nevitt, Lui, & Covsinsky, 2001) at follow-up. However, the observed effects of PA on cognition tend to be influenced by follow-up intervals. The majority of studies reporting a significant association between activity and cognition examined outcomes approximately 2 to 6 years after baseline (e.g. Buchman et al., 2012; Lytle et al., 2004; Middleton et al., 2011). Studies examining the effects of baseline PA on cognitive abilities over a relatively longer follow-up intervals (e.g. >10) typically yield mixed results (Morgan et al., 2012; Rovio et al., 2005; Rovio et al., 2010). It is possible that change or fluctuation in PA levels are better able to predict cognitive performance, and that, with longer follow-up individuals are being misclassified, as PA levels are more likely to have changed over greater periods of time (Morgan et al., 2012).

Middleton, Barnes, Lui, and Yafee (2010) found that women who were sedentary in younger years, and became physically active in later life had a lower risk of developing cognitive impairments than those who remained inactive. Lindwall et al. (2012) analyzed four different longitudinal data sets including the OCTO-Twin study, Long Beach Longitudinal Study (LBLS), Seattle Longitudinal Study Sample (SLS) and Victoria Longitudinal Study Sample (VLS) in a co-ordinated manner, employing change in PA since baseline as a time-varying covariate. The authors report that change in PA was significantly associated with change in reasoning ability across all four data sets, change in memory in two of the studies (OCTO-Twin and VLS), change in semantic knowledge in one study (OCTO-Twin), and change in fluency in two of three data sets (VLS and SLS), in the expected direction. However, when employing more traditional longitudinal analyses, PA level at baseline was only associated with less decline in fluency in

two of the three studies. In light of these findings, a more proximal indicator of PA levels, such as occasion specific PA may be a more viable predictor of cognitive outcomes. Specifically, understanding how fluctuations in activity levels over time affect cognitive abilities can address the mixed findings produced by longer follow up periods in longitudinal design.

The meta-analyses conducted by Blondell, Hammersley, Mather, and Veerman (2014) identified the Mini Mental State Examination (MMSE), a screening tool for general cognitive impairment, as the most commonly used cognitive outcome variable in the longitudinal studies included. This measure has utility in identifying those with moderate to severe cognitive impairments; however, it is not sensitive to subtler decline. As a result of ubiquitous MMSE use, there is less research identifying particular domains of functioning that are impaired. For example, some studies have indicated that EF (Colcombe & Kramer, 2003; Lindwall et al., 2012), episodic memory, and processing speed (Angevaren et al., 2007; Buchman et al., 2012) are positively influenced by participation in PA, while semantic memory is relatively unchanged (Buchman et al., 2012; Lindwall et al., 2012). This trend elucidates the need to include measures of cognitive abilities specific to the various domains of cognitive functioning susceptible to decline – as well as those potentially sensitive to the beneficial effects of exercise.

**Stress and Cognition**

The hypothalamic-pituitary-adrenal axis (HPA) is activated in response to situations acutely interpreted as stressful. This is followed by a cascade of events that signal the release of glucocorticoids and catecholamines (i.e., stress hormones). In response, metabolic and immune systems alter functioning to mobilize energy so that the organism can respond to the demands of the situation (Tsatsoulis & Fountoulakis, 2006). This adaptive response to stress is termed "allostasis", or stability through change (McEwen, 1998). If this response is chronic and

continuous, the system becomes inefficient, resulting in “allostatic load”. This leaves one susceptible to a myriad of tertiary diseases (McEwen & Stellar, 1993). Stress hormones are able to cross the blood-brain barrier, with the highest occurrence of glucocorticoid receptors located in the hippocampus and frontal lobes (Lupien, Maheu, Fiocco, & Schramek, 2007). The insidious effect of chronic stress on the hippocampus has been extensively studied (Lupien et al., 1996; Seeman, McEwen, Roew, and Singer, 1997). Specifically, the glucocorticoid-cascade hypotheses (Sapolsky, Krey, & McEwen, 1986) suggests that exposure to glucocorticoids over extended periods of time degrades hippocampal receptors leading to neuronal death, disruption in the HPA regulatory loop, and vulnerability to acute stressors. This atrophy has functional consequences, such as reduced episodic and declarative memory. The pre-frontal cortex is similarly affected by stress. Stress leads to chemical alterations acutely, and architectural changes over extended periods of exposure, both of which subsequently influence EF (Arnsten, 2009; Cerqueira, Mailliet, Almeida, Jay, & Sousa, 2007). These effects are speculated to be magnified in older adults, as less efficient biological systems are expected to increase vulnerability to stress (McEwen & Morrison, 2013).

These damaging effects were demonstrated in a longitudinal study with older adults aged 60 to 90 years (Lupien et al., 1996). Basal cortisol levels were measured annually, multiple times across a 24-hour period, for 3 to 6 years. Employing the cortisol slopes of participants over the duration of the study, and the average of the last annual 24-hour cortisol collection, the authors classified 23.5% of subjects as hyper-cortisol secretors (positive slope and recently high cortisol levels, indicated by surpassing 12.5/µg/ml/h of cortisol on their last average 24 hour measure; PSH), 56.8% of the sample as increasing in cortisol and recently moderate (PSM) and 19.6% of individuals as decreasing, and recently low (DL). The authors reported that PSH group had 14%

less hippocampal volume on average, when compared to the DL group. Importantly, increasing cortisol slopes predicted cognitive decline, as the PSH group scored significantly lower on explicit memory and selective attention tasks than the PSM group and DL group, while the DL group performed just as well as young healthy subjects. The authors' hypothesis that the cortisol slope (as opposed to a static measure of cortisol) would better predict cognition was supported, as there was no relationship between the last annual cortisol measure and cognitive abilities. However, the authors note that the recent static measure of stress was an important determinant, as there were significant differences between participants with increasing cortisol levels who had recently high and recently moderate annual cortisol levels (PSM and PSH group). These findings suggest that cumulative exposure to stressors over time has detrimental effects on cognitive abilities, and leaves one more vulnerable to the effects of current stressors.

However, other studies have demonstrated that purely acute stressors influence cognitive abilities. Measures of stress in these studies are often highly contrived and lack ecological validity. For example, endogenous cortisol manipulation (Beckwith, Petros, Scaglione, & Nelson, 1986; Newcomer et al., 1999) and lab induced acute psychosocial stressors (Bohnen, Houx, Nicolson, & Jolles, 1990; Kirschbaum et al., 1996) are typically used to manipulate stress. However, there is a dearth of aging literature examining self-reported measures of naturally occurring stressors and cognitive outcomes in particular. The limited studies that do exist suggest that cognitive consequences are incurred. For example, older adults report more memory failures (Neupert, Almeida, & Mroczek, 2006) and exhibit poorer working memory performance (Sliwinski, Smyth, Hofer, & Stawski, 2006) on days when more stressful events are reported. Both studies utilized hierarchical linear modeling to examine coupled change between daily stress and memory in order to examine how these variables change together. Specifically,

changes in cognitive ability were predicted by daily fluctuations in reported levels of stress. This daily-diary methodology demonstrates the stress-cognition association on a relatively short time scale (i.e., weeks), although coupled change in stress and cognition has not been examined over longer time intervals, such as years.

**Mechanisms and the Interaction between Physical Activity and Stress**

Exercise and stress tend to exert opposing influences on similar biological pathways. As a result, exercise is speculated to buffer against the negative effects of stress, positively influencing brain health and cognition. At the neurological level, PA exposes neurons to metabolic stress eliciting an adaptive and protective response. Brain-derived neurotrophic factor (BDNF) is a protein found in the hippocampus and cerebral cortex (Lommatzsch et al., 2005) that is up-regulated during exercise (Rothman & Mattson, 2013). It is generally established that BDNF facilitates neuronal survival, differentiation, axonal and dendritic growth, long-term potentiation (LTP), and synaptic transmission (Knaepen, Goekint, Heyman, & Meeusen, 2010). This typically leads to improvements in learning and memory (Rothman & Mattson, 2013). For example, PA is associated with higher levels of BDNF in rodents (Adlard, Perreau, Engesser-Cesar, & Cotman, 2004; Cotman & Berchtold, 2002) and improved performance on maze-training tasks (Berchtold et al., 2005). Recent studies with human populations also report an increase in serum BDNF and cognitive performance after exercise (Erickson et al., 2011; Ferris, William, & Shen, 2007; Griffin et al., 2011). Conversely, glucocorticoids secreted in response to stress hinder the production of BDNF and exacerbate neuropathological changes related to dementia (Nation et al., 2011). In animal models, chronic and unpredictable stress has been demonstrated to decrease BDNF levels in the prefrontal cortex and hippocampus (Lui et al., 2013). Insufficient BDNF can result in vulnerability to neurodegeneration (Rothman & Mattson,

2013). It is plausible then, that PA reduces the deleterious effects associated with stress and increasing age (Rothman & Mattson, 2013; Kwon et al., 2013). Neuroprotective effects are speculated to be due to the modulation of synaptic plasticity regulated by BDNF.

Moreover, exercise may reduce sensitivity to stress through altering HPA functioning (see Crews & Landers, 1987). The cross-stress adaptation hypothesis postulates that an improved physiological response during exercise (i.e., a "good" stressor) is extended to HPA adaptation during psychosocial stress (Sothmann et al., 1996). This is corroborated by lower cortisol and catecholamine levels in response to stressful stimuli in fit individuals (Traustadottir, Bosch, & Matt, 2005), and a decrease in blood pressure, seen only in participants exercising just prior to a lab induced stressor (Hammer, Taylor, & Steptoe, 2006). However, findings regarding the buffering effects of physical fitness on stress reactivity are less consistent, while acute bouts of exercise typically prove to be beneficial (Hamer, 2012). Improvement in hemodynamic functioning in response to mental stress is thought to be one of the primary contributing factors to the stress-buffering effects of exercise (Hamer, 2012). Additionally, immune system functioning is altered by stressors. Inflammation is common in chronically stressed individuals, however exercise increases interleukin (IL)-6, combating inflammatory factors (Pedersen, 2011). For example, habitual PA for 10 years is associated with inflammatory markers (Hamer et al., 2012). Interestingly, there is more evidence for a buffering effect of habitual, chronic PA on immune system functioning, than there is for acute bouts (Hamer, 2012). Lastly, stress has profound metabolic consequences. Excess glucocorticoids induce a state of leptin resistance, increasing the likelihood of obesity. This condition is often accompanied by metabolic syndrome, characterized by insulin resistance, and strongly associated with inactivity (Tsatsoulis & Fountoulakis, 2006). In light of the findings that implicate low-levels of activity in

cardiometabolic disease and increases in allostatic load (Seeman, Singer, & Rowe, 1997), is quite likely that PA exerts its neuroprotective effects through a multitude of protective biological alterations.

In animal models, evidence supporting the buffering effects of physical activity on stress has been demonstrated with controlled designs (e.g., Aguiar et al, 2011; Kwon et al., 2013). Less is known about the interaction between stress and PA with respect to cognitive outcomes in human populations, although there is evidence to suggest PA is indeed protective. Heaney, Caroll and Phillips (2014) demonstrate that in individuals with a higher stress incidence score, and who reported less than 1 hour of exercise per week had a significantly higher cortisol: Dehydroepiandrosterone ratio compared to their physically active counterparts. However, cognitive performance was not assessed in this study. When examining cognition in particular, Head, Singh, and Bugg (2012) report that higher lifetime trauma is associated with poorer memory and reduced hippocampal volume only in those reporting low to average levels of PA. Moreover, allostatic load at baseline has been associated with cognitive decline 2.5 years later in participants reporting relatively less activity (Seeman et al., 1997). This evidence encourages future examination into the possible protective effects of PA against stress related cognitive decline.

**Summary**

A review of the literature reveals that both PA and stress have been linked to cognitive outcomes with aging. In order to understand processes that change over time, such as fluctuations in PA and stress and their relationship to decline in cognitive abilities, longitudinal investigation is required. Although baseline measures of PA are associated with cognitive outcomes in the elderly, this association becomes obscured with longer follow-up periods. More

proximal indicators of activity, such as closer follow-up intervals or measures of change in PA since baseline have demonstrated to be more reliable predictors of cognitive performance. Similarly, the stress literature demonstrates a coupled association between cognitive abilities and stressors on a daily level (Sliwinski, et al., 2006; Neupert, 2003), however fluctuations in stress and the effects on cognition have not been explored over longer periods of time (i.e., years). Additionally, fewer longitudinal studies employ measures of specific cognitive abilities as outcomes (e.g., EF, episodic memory, and processing speed) compared to global measures such as the MMSE. Moreover, naturally occurring self-reported stressors are infrequently utilised as predictors of cognitive decline, despite their ecological validity. Lastly, beyond animal based research there are only a few publications addressing the interaction between PA and stress in human subjects, and typically these studies to not include older adults, who are potentially more vulnerable to stress.

## The Current Study

The present investigation addresses these concerns. Coupled change Multilevel Models (MLM) examining the effects of PA, stress, and their interaction were fit to two population based longitudinal data sets. PA levels and incidence of naturally occurring stressors were reported by participants at each measurement occasion. In addition to the MMSE, both episodic memory and perceptual speed (a type of processing speed, indicating the speed in which one can carry out simple, automatic tasks) were modeled as outcomes. Both individual averages (between-person effects; BP) and occasion specific fluctuations in levels of PA and stress (within-person effects; WP) were modeled in relation to cognitive outcomes. That is, the present analyses included WP predictors, indicating whether the participant was exercising or stressing more or less than usual (their mean) at each occasion. Additionally, the interaction between stress and PA was examined at the BP level, the WP level, and across levels (See Statistical Analyses section and Hypotheses 3 and 4).

The present study is a coordinated investigation of two longitudinal studies. This method is more efficient and robust as it allows researchers to implement the same analyses on multiple datasets, addressing both reproducibility and generalizability (Hofer & Piccinin, 2009). Analogous variables across data sets can be modelled in the same way, facilitating a direct comparison of results. In the present investigation, data from the Memory and Aging Project (MAP) and Longitudinal Aging Study Amsterdam (LASA) were modeled. Both data sets contained comparable measures of PA and stress, and similar cognitive outcomes that measured perceptual speed, episodic memory, and general decline (MMSE).

### Hypotheses

**Between-Person Hypotheses.** It was expected that individuals with higher average PA scores (i.e., mean PA across occasions) would perform better on cognitive tasks, compared to

individuals with lower average PA scores (Hypothesis 1A). Additionally, it was expected that individuals with lower average stress incidence scores (i.e., mean stress level across occasions) would perform better on cognitive tasks, compared to individuals with higher average stress incidence scores (Hypothesis 1B).

**Within-Person Hypotheses.** It was expected that on occasions when individuals are more active than usual, they would perform better on cognitive tasks compared to occasions when they are less active (Hypothesis 2A**).** Also, it was expected that on occasions when individuals reported fewer stressors than usual, they would perform better on cognitive tasks compared to occasions when they report more stressors than usual (Hypothesis 2B).

**Interaction Hypotheses.**

***Between-Person stress.*** It was anticipated that the effects of higher average stress (BP effects) would be mitigated by higher average PA (BP) (Hypothesis 3A), and on occasions when individuals are exercising more than usual (WP) (Hypothesis 3B).

***Within-Person stress.*** Also, it was anticipated that the effects of occasion specific stress (WP effects) would be mitigated by generally higher average PA (BP) (Hypothesis 4A), and on occasion when individuals are exercising more than usual (WP) (Hypothesis 4B).

# Method

## Participants

The current analyses are based on the MAP data collected at Rush University Medical Center in Chicago, Illinois, and the LASA data, conducted by researchers at the VU University Medical Center in the Netherlands. The primary emphasis of MAP is to understand how decline in cognitive and motor functioning are related to risk of AD. MAP began collecting data in 1997 and continues presently. At its inception, LASA emphasized understanding the function and well-being of older Dutch individuals through a multidisciplinary lens, with data collection beginning in 1992 and ongoing.

In MAP, data were collected from elderly adults ($n$ = 1,853) living in continuous care retirement communities throughout northeastern Illinois. Data were collected during home visits so that co-morbidities common in the population were well represented, and follow-up rates were enhanced. The average age at baseline was 79 ($SD$ = 7.31, range = 55-86). Data from the cohort were collected on an annual basis. On average, participants had data for 4 occasions ($SD$ = 3.57), ranging from 1 to 18 years of follow-up. The sample consisted of 485 males and 1367 females, with 14.73 ($SD$ = 3.16, range = 0-28) years of education on average. Individuals with dementia at baseline were not excluded from analyses (n = 100).

The LASA cohort was based on a sample of older adults ($n$ = 4,109), aged 68 years old on average at baseline ($SD$ = 9.04, range = 55-86). In order to obtain a nationally representative sample, data collection occurred in three geographic regions in The Netherlands, including the Protestant north, the Catholic south, and secular regions, as well as from both rural and urbanized areas within these regions. Participants were recruited from municipal registries (See Huisman et al., 2011 for an extended review of cohort profiles). The present investigation includes data from the same cohort of individuals followed-up every 3 years. Similar to MAP data collection,

interviews took place in the participant's home. On average, participants had data for 4 follow-up occasions (*SD* = 2, range = 1-7), spaced 3 years apart (yielding a range of 1-21 years of data collection, similar to the 18 years of MAP data collected annually). The sample consisted of 2,128 men and 1,981 females, with 9.15 (*SD* = 3.4, range = 5-18) years of education on average. Individuals with dementia at baseline were not excluded from analyses.

## Measures

**Cognitive Outcomes.** In MAP and LASA, perceptual speed, episodic memory, and the MMSE were overlapping cognitive measures, facilitating coordinated analyses. That is, MAP measured perceptual speed using the Symbol Digit Modalities Test (SDMT) and LASA employed an analogous Coding task. Episodic memory was assessed using the Word List I, Immediate (WLI) recall test in MAP and the 15 Word Test (15WT) in LASA. Both studies administered the MMSE to participants. Participants' raw scores on these measures were used as outcomes in analyses. Cognitive measures are explained in further detail below.

***Perceptual Speed.*** In MAP, perceptual speed was measured with the oral version of the SDMT (Smith, 1982). This measure requires participants learn to associate digits with abstract symbols. Participants referred to a key that displayed a series of symbols paired with a corresponding number from 1 to 9. Participants viewed the symbols in order, and were asked to verbalize the matching number based on the key provided. They were allocated 90 seconds to translate as many symbols as possible. The total score was computed based on the number of correctly identified symbols. Symbol substitution measures have been demonstrated to be stable and sensitive to cognitive impairments associated with aging and AD (Salthouse, 2000).

In LASA, perceptual speed was also measured with an oral version of a coding task. In LASA, the specific task administered was an adjusted version of the Alphabet Coding Task-15

(Savage, 1984). Similarly, in this task, two rows of characters were displayed and the participants were expected to complete as many combinations as possible, by naming the corresponding character. However, the LASA coding task differed from MAP, in that it involved letter-letter pairs (consonants only, no vowels) rather than symbols and digits.

***Memory.*** Episodic memory was assessed with the Word List I, immediate recall, adopted from the Consortium to Establish a Registry for AD (CERAD) set of neuropsychological performance tests (Moms et al., 1995). A list of 10 semantically unrelated words were read aloud to participants one at a time, requiring immediate recall of as many words as possible after each trial. Three trials were administered in this fashion, with the order of the 10 words being randomized each time. Performance scores were determined by the total number of words recalled correctly in all 3 trials.

In LASA, episodic memory was assessed with the 15WT, which is the Dutch version of the Auditory Verbal Learning Test (AVLT; Deelman et al., 1980; Rey 1964; Saan & Deelman, 1986). Participants were instructed to listen to a list of 15 words, and immediately recall as many of the words as possible after each learning trial (3 in total). In LASA, two parallel versions of the 15WT were administered so that retest effects were not present at follow-up. The maximum score of the three trials was used as the cognitive outcomes variable in analyses. This approach is recommended by LASA coordinators, and has been the approach implemented in past studies.

***MMSE.*** The MMSE was administered in both MAP and LASA. This is a widely used, 30-item standardized screening measure of global cognitive functioning and dementia. The measure has demonstrated short-term temporal stability and concurrent validity, as it has been demonstrated to be highly correlated with Verbal IQ ($r$ = .78) and Performance IQ ($r$ = .66) of the Wechsler Adults Intelligence Scale (WAIS) (Folstein, Folstein, & McHugh, 1975). The

MMSE consist of 20 items assessing participant's orientation in time, orientation in place, registration of 3 words, attention and calculation, recall of three words, language, and visual construction.

**Physical Activity.** In MAP, PA engagement was assessed with a questionnaire adapted from the 1985 National Health Interview Survey. Self-reported minutes spent engaging in walking, gardening, calisthenics, bike riding, and swimming were summed and expressed as *hours of activity per week*.

In LASA, a comparable composite variable was constructed based on the LASA Physical Activity Questionnaire (LAPAQ). This measure has been validated against 7-day physical activity diaries ($r$ = .68) and 7-day pedometer counts ($r$ = .56) in a subsample of 439 LASA participants (Stel et al., 2004). Specifically, respondents were asked how often (frequency) and for how long (duration, in minutes) in the previous *two weeks* they had engaged in walking outdoors, bicycling, gardening, light household work, heavy household work, and two sports activities. In order to make the variable more comparable to MAP which includes only 5 activities, the two household work questions were dropped as they were deemed least similar to the types of PA assessed in MAP. Additionally, the frequency and duration of each activity were multiplied to yield the total minutes per two weeks spent in each activity. In order to obtain hours of activity per week (comparable to MAP), the scores for each activity were divided by two. These scores were summed across activities, yielding the total amount of PA in minutes per week. The totals were then converted to hours (divided by 60), so that the LASA PA variable similarly referred to the total hours per week engaged in PA.

**Stress.** MAP and LASA both administered a version of the Negative Life Events Questionnaire (NLE) at follow-up occasions, inquiring about events that had occurred since the

last interview (annually in MAP, every 3 years in LASA). In MAP, participants were asked about 18 different events, ranging from financial need and personal illness, to death of a loved one. LASA inquired about 12 similar events. In both data sets, participants were given 1 point for every event they had experienced since the past interview, and responses were summed at each measurement occasion to obtain a total score.

**Statistical Analysis**

In order to understand the BP and WP effects of PA, stress, and their interaction on cognitive outcomes, a series of multilevel models (MLM) were estimated. Inherently, time varying predictors (TV; where each individual, *i*, is assessed at a particular time, *t*) contain both BP and WP effects which can be parsed out of the original measure (Hoffman, 2015; Singer & Willet, 2003). The *individual's mean across waves* represents the BP effects, and *occasion specific* deviations from each participant's unique mean represent WP effects (i.e., occasions when participants are scoring higher or lower than usual). Therefore, in order to address both the BP and WP effects of PA and NLE (i.e., TV predictors) in the present study, each participant's mean PA and mean NLE scores were subtracted from their occasion specific PA score and NLE score, respectively (referred to as person-mean centering, see Hoffman, 2015). Thus, the variables WP PA and WP NLE were created, representing the WP effects of the two predictors. WP covariation between two variables (such as a predictor and an outcome) would indicate that scores "travel together" over time (Sliwinski & Buschke, 2004). Regarding the BP effects, each person's mean PA and NLE scores were centered upon sample averages (hereinafter referred to as BP PA, and BP NLE, respectively) for ease of coefficient interpretation (e.g., a BP PA score of 0 represents a participant whose mean PA level is equal to the sample's mean PA, while a positive score represents a participant with higher average PA than the population average.) In

addition to the nuanced advantages of modeling both BP and WP effects, compared to traditional approaches, MLM can more flexibly account for data that is missing at random (Quene & van den Bergh, 2004) and does not require balanced interval time scheduling amongst participants.

Generally in MLM, a unique trajectory for each participant in the study is determined at the first level of analysis (See Model X). Therefore, TV predictors (e.g., wave, WP PA and WP NLE) are specified at the first level, or WP level. In the hypothetical model, three parameters are estimated, $\beta_{0i}$ and $\beta_{1i}$, and $e_{ti}$. Respectively, these reflect the intercept for person *i*, rate of change for person *i*, and the residual variance for person *i* at time *t*. (Sliwinki, & Bushke, 2004). .

Level 1: $Cog_{ti} = \beta_{0i} + \beta_{1i}(TV_{ti}) + e_{ti}$

Level 2: $\beta_{0i\ (intercept)} = \gamma_{00} + U_{0i}$

$\beta_{1i\ (slope)} = \gamma_{10} + \mathbf{U_{1i}}$ (Model X)

The Level-1 (time) model is nested within a second level (person), such that the distributions of these person specific parameters are modeled around population averages. Therefore, the population parameters (*fixed-effects*) inform population-level trends in, for example, the intercept or slope ($\gamma_{00}$ and $\gamma_{10}$, respectively). Idiosyncratic deviations from these parameters ($U_{0i,}$ and $U_{1i}$, respectively) indicate whether there is significant individual variation from population averages. The level-2 slope variance (See bolded term in Model X) can be constrained so that all participants are assumed to be represented by the fixed effects, or specified as freely estimated, so that a unique trajectory for each individual is computed. To determine whether individuals significantly differ in their slopes, the deviances of models with and without this variance component specified are compared. When included, there are three variance components, or *random effects* represented in Model X: the BP level-2 random intercept variance (denoted $\tau_{00}$), the BP level-2 random slope variance (denoted $\tau_{01}$), and the WP level-1

residuals variance (denoted $\sigma^2$). These effects are sources of variance to be explained at each level.

In the present study, separate, yet identical analyses were employed for each cognitive outcome variable within each data set (i.e., MAP and LASA models for perceptual speed, episodic memory, and MMSE). TV predictors were modeled at the first level of analysis (the WP level), and time invariant (TIV) predictors were modeled at the second level (the BP level), according to the hypotheses.

Initially, an unconditional model (without predictors; Model 0) was fit to the data to determine the percent of BP and WP variance in each cognitive outcome. Then, the effects of time were added to the model (Model 1). A demographic model served as the base model (Model 2), in which the variables of interest were subsequently added (i.e., PA in Model 3A and 3B; NLE in Model 4A and 4B, and the interaction terms in Model 5). In order to determine if the inclusion of a random BP slope variance fit the data for both WP PA and WP NLE, models with (3B and 4B, respectively) and without (3A and 4A, respectively) this variance component were compared. (Note, bold font indicates that only the B version of the model specifies the bolded random effect, while the A is the fixed effects only).

Level 1: $Cog_{ti} = \beta_{0i} + e_{ti}$

Level 2: $\beta_{0i} = \gamma_{00} + U_{0i}$

Model 0

Level 1: $Cog_{ti} = \beta_{0i} + \beta_{1i}(Time_{ti}) + e_{ti}$

Level 2: $\beta_{0i} = \gamma_{00} + U_{0i}$

$\beta_{1i} = \gamma_{10} + \mathbf{U_{1i}}$

Model 1A and 1B

Level 1: $Cog_{ti} = \beta_{0i} + \beta_{1i}(Time_{ti}) + e_{ti}$

Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}(AgeBL_i) + \gamma_{02}(SexM_i) + \gamma_{03}(Edu_i) + U_{0i}$

$\beta_{1i} = \gamma_{10} + \gamma_{11}(AgeBL_i) + \gamma_{12}(SexM_i) + \gamma_{13}(Edu_i) + U_{1i}$

Model 2

Level 1: $Cog_{ti} = \beta_{0i} + \beta_{1i}(Time_{ti}) + \beta_{2i}(WP\ PA_{ti}) + e_{ti}$

Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}(AgeBL_i) + \gamma_{02}(SexM_i) + \gamma_{03}(Edu_i) + \gamma_{04}(BP\ PA_i) + U_{0i}$

$\beta_{1i} = \gamma_{10} + \gamma_{11}(AgeBL_i) + \gamma_{12}(SexM_i) + \gamma_{13}(Edu_i) + \gamma_{14}(BP\ PA_i) + U_{1i}$

$\beta_{2i} = \gamma_{20} + \mathbf{U_{2i}}$

Model 3A and 3B

Level 1: $Cog_{ti} = \beta_{0i} + \beta_{1i}(Time_{ti}) + \beta_{2i}(WP\ NLE_{ti}) + e_{ti}$

Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}(AgeBL_i) + \gamma_{02}(SexM_i) + \gamma_{03}(Edu_i) + \gamma_{04}(BP\ NLE_i) + U_{0i}$

$\beta_{1i} = \gamma_{10} + \gamma_{11}(AgeBL_i) + \gamma_{12}(SexM_i) + \gamma_{13}(Edu_i) + \gamma_{14}(BP\ NLE_i) + U_{1i}$

$\beta_{2i} = \gamma_{20} + \mathbf{U_{2i}}$

Model 4A and 4B

Level 1: $Cog_{ti} = \beta_{0i} + \beta_{1i}(Time_{ti}) + \beta_{2i}(WP\ NLE_{ti}) + \beta_{3i}(WP\ PA_{ti}) + \beta_{4i}(WP\ NLE_{ti*}\ WP\ PA_{ti}) + e_{ti}$

Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}(AgeBL_i) + \gamma_{02}(SexM_i) + \gamma_{03}(Edu_i) + \gamma_{04}(BP\ NLE_{i*}BP\ PA_i) + U_{0i}$

$\beta_{1i} = \gamma_{10} + \gamma_{11}(AgeBL_i) + \gamma_{12}(SexM_i) + \gamma_{13}(Edu_i) + U_{1i}$

$\beta_{2i} = \gamma_{20} + \gamma_{21}(BP\ PA_i) + U_{2i}$

$\beta_{3i} = \gamma_{30} + \gamma_{31}(BP\ NLE_i) + U_{3i}$

$\beta_{4i} = \gamma_{40} + U_{4i}$

Model 5

For all the models, $Cog_{ti}$ is individual *i*'s performance on the cognitive measure at time *t.* $\beta_{0i}$ is the intercept for person *i,* $\gamma_{00}$ represents the main effects of the intercept, and $\gamma_{01}$- $\gamma_{04}$ correspond to the fixed effects on the random intercept. $\beta_{1i}$ reflects person *i*'s slope, $\gamma_{10}$ represents the main effects of time, and $\gamma_{11}$- $\gamma_{14}$ correspond to the fixed effects of predictors on the random slope. Thus, $\gamma_{04}$, and $\gamma_{14}$ represents the effects of BP PA (in Model 3B, H1A) or BP NLE (in Model 4B, H1B) on the intercept and slope, respectively.

In Models 3B and 4B, $\beta_{2i}$ represents either person *i*'s WP PA slope or WP NLE slope, respectively. $\gamma_{20}$ corresponds to the main effects of WP PA (in Model 3B, H2A), or WP NLE (in Model 4B, H2B). In Model 5, the effects of $\gamma_{04}$ reflect the interaction between BP NLE and BP PA (H3A) on the intercept, and $\gamma_{31}$ corresponds to the effects of PA WP on BP NLE (H3B). $\boldsymbol{\gamma_{21}}$ corresponds to the effects of BP PA on WP NLE (i.e. H4A), and $\gamma_{40}$ refers to effects WP PA on WP NLE (H4B).

Coupled change MLMs were conducted in R, using full information maximum likelihood (FIML) in order to compare models that contain both fixed and random effects. Specifically, the Wald Test p-values that correspond to the ratio of an estimate to its standard error were used to

determine the significance of the fixed effects. A likelihood ratio test (-2LL) for nested model comparison (i.e., a fixed-slope model would be nested within a model that specifies a random slope) was used to test the significance of the level-2 random effects (See Hoffman, 2015).

In MAP, wave was used as the time metric in the longitudinal model, thus, baseline is represented by a value of 0, the first annual follow-up occasion as 1, and so forth. Wave was also used as the time metric in the LASA models. However, each wave represented 3 years since baseline as mentioned. The demographic variables were centered upon the sample mean for ease of interpretation. That is, the intercept and slope represent expected baseline performance and annual rate of change for a female participant entering the study at 79 years of age, with 14.73 years of education in MAP, and a female participant entering the study at 68 years of age, with 9.15 years of education in LASA.

# Results

## Descriptive Statistics

**Physical Activity.** In *MAP*, individuals exercised 2.94 (*SD* = 3.5, range = 0 - 43.5) hours per week, averaged over individuals and occasions, with 45% of the variance at the BP level (calculated with the intraclass correlation; ICC). In *LASA*, participants exercised 1.18 hours per week on average (*SD* = 4.13, range = 0 – 66), with 51% of the variance at the BP level. In LASA four participants scoring higher than 70 hours per week (averaging 10 hours per day) were regarded as outliers and eliminated from analyses.

**Stress.** In *MAP*, the sample mean NLE score of the sample was 2.46 (*SD* = 1.91, range = 0 - 17), with 31% of the variance BP. In *LASA*, the mean NLE score was 0.18 (*SD* = 0.59, range = 0 - 6), with 61% of the variance BP.

**Cognition.** Regarding perceptual speed, on average, *MAP* participants scored 35.75 (*SD* = 13.13, range = 0 - 77) on the SDMT. In *LASA*, the average Coding score was 25.28 (*SD* = 6.51, range = 5.33 - 43.44). Regarding episodic memory, participants typically recalled 17.37 (*SD* = 5.49, range = 0 - 30) words on the WLI immediate recall task in MAP. In *LASA*, the mean score on the 15WT was 8.87 (*SD* = 6.51, range = 0 - 15), reflecting average episodic memory performance. On average, *MAP* participants scored 26.42 (*SD* = 5.14, range = 0 - 30) on the MMSE and *LASA* participants scored 27.85 (*SD* = 2.14, range = 0 - 30).

## Unconditional Models

Initially, fully unconditional models (Model 0) were fit for each cognitive outcome in order to partition the BP and WP variance for each. In *MAP*, 73%, 69%, and 56% of the variance was at the BP level for SDMT, WLI and the MMSE, respectively. In the same manner, 68%, 45%, 37% of the variability in Coding, 15WT, and the MMSE were at the BP level in *LASA*. The

ICCs of the cognitive variables suggest that there is sufficient variability at the WP level, encouraging subsequent analysis of time varying factors.

**MAP.** The effects of time were then added to Model 0. When compared to a fixed-effects only model (Model 1A), a random time slope model (Model 1B) significantly improved the fit for the SDMT, $\Delta\chi^2$ (2) = 1587.1, $p < .001$, WLI, $\Delta\chi^2$ (2) = 1420, $p < .001$, and MMSE, $\Delta\chi^2$ (2) = 5187.9, $p < .001$. This suggests that there is significant variability between individual trajectories. Results from Model 1B indicate that on average, SDMT, WLI, and MMSE declines over time are statistically significant ($p < .001$), as expected (See Table 1).

**LASA.** When compared to a fixed-effects only model (Model 1A), the random time slope model (Model 1B) significantly improved the fit for Coding, $\Delta\chi^2$ (2) = 80, $p < .001$; 15WT, $\Delta\chi^2$ (2) = 6.55, $p < .001$, and the MMSE, $\Delta\chi^2$ (2) = 358, $p < .001$. Like *MAP*, Model 1B indicates that Coding, 15WT, and MMSE are also significantly declining over time ($p < .001$) (See Table 1).

**Demographic Models**

**MAP.** Controlling for baseline age, educational attainment and sex, with female being the reference group (Model 2), significantly improved the model fit for all cognitive outcomes when compared to the random time slope only model (Model 1B) (SDMT, $\Delta\chi^2$ (6) = 543.2, $p < .001$, WLI, $\Delta\chi^2$ (6) = 483.82, $p < .001$, and MMSE, $\Delta\chi^2$ (6) = 277.77, $p < .001$). Participants entering the study at a relatively older age, and males scored lower on all baseline cognitive outcomes, while education was positively associated with baseline cognitive scores. Additionally, age at entry was negatively associated with cognitive decline across all outcomes. However, men declined less rapidly on the WLI**.** Sex and education were not predictive of decline on any of the other cognitive outcomes (See Table 2).

**LASA.** Model 2 fit the data significantly better compared to Model 1B for all of the cognitive outcomes (Coding, $\Delta\chi^2$ (6) = 67, $p < .001$, 15WT, $\Delta\chi^2$ (6) = 43, $p < .001$, and MMSE, $\Delta\chi^2$ (6) = 129, $p < .001$ ). Age at entry was associated with lower baseline Coding scores, however unexpectedly predicted higher MMSE scores at baseline. Additionally, education was positively associated with cognitive performance across all LASA outcomes at baseline, and male participants tended to score lower on Coding and the WLI. Older age at entry was associated with steeper declines in Coding and MMSE scores. Moreover, education was positively associated with the slope of MMSE scores (See Table 2).

**Physical Activity Models**

**MAP.** A fixed-effects only model (Model 3A) was compared to a model with the inclusion of a random variance component ($U_{2i}$) for WP PA (Model 3B). Model 3B was a significantly better fit for the SDMT test, $\Delta\chi^2$ (3) = 13.49, $p < 0.001$, WLI, $\Delta\chi^2$ (3) = 14, $p < 0.001$, and MMSE, $\Delta\chi^2$ (3) = 43, $p < 0.001$, suggesting that after controlling for the effects of time, WP fluctuations in PA predict cognitive abilities differentially across individuals.

BP PA was positively associated with the intercept of SDMT (*B*[SE] = 0.23[0.09], t(1781) = 2.57, $p = .01$), and WLI, *B*[SE] = 0.10[0.04], t(1853) = 2.81, $p = .005$. Additionally, BP PA was positively associated with the slope of all cognitive outcomes (SDMT; *B*[SE] = 0.06[0.02], t(755) = 4.05, $p < .001$, WLI, *B*[SE] = 0.03[0.01], t(912) = 3.79, $p < .001$, and MMSE, *B*[SE] = 0.04[0.01], t(836) = 3.84, $p < .001$) (See Table 3, and Figure 1).

WP PA was also significantly associated with all cognitive outcomes in MAP (SDMT; [SE] = 0.06[0.02], t(754) = 4.05, $p = .01$, WLI; *B*[SE] = 0.03[0.01], t(487) = 2.11, $p = .03$, and MMSE; *B*[SE] = 0.03[0.01], t(193) = 2.5, $p = .01$) in the expected direction (See Table 3, and Figure 2).

**LASA.** A fixed-effects only model (Model 3A) was compared to a model with the inclusion of a random variance component ($U_{2i}$) for WP PA (Model 3B). Model 3B did not fit the data significantly better for Coding, $\Delta\chi^2$ (3) = 0.19, $p$ = 0.97, or 15WT, $\Delta\chi^2$ (3) = 4.40, $p$ = 0.22, although it was a better fit for the MMSE, $\Delta\chi^2$ (3) = 15.70, $p$ = 0.001.

BP PA was not associated with any cognitive outcomes (See Table 3, and Figure 3). WP PA was associated with Coding, *B*[SE] = 0.03[0.01], t(1182) = 2.32, $p < 0.01$), and approached significance for the MMSE, *B*[SE] = 0.01[0.00], t(288) = 1.91, $p$ = .06) in the expected direction (See Table 3, and Figure 4).

**Stress Models**

**MAP.** A fixed-effects only model (Model 4A) was compared to a model with the inclusion of a random variance component ($U_{2i}$) for WP PA (Model 4B). Model 4B fit the data better for SDMT, $\Delta\chi^2$ (3) = 9.78, $p$ = .02, WLI, $\Delta\chi^2$ (3) = 8.24, $p$ = .04, and MMSE, $\Delta\chi^2$ (3) = 15.8, $p$ = .001. Thus, the extent to which more stress than usual influences cognitive abilities varies across people, encouraging the exploration of moderators. However, neither BP NLE nor WP NLE were associated with the intercept or slope for any of the cognitive outcomes in MAP (See Table 4, Figure 5, and Figure 6).

**LASA.** The fixed-effects only model (Model 4A) was compared to a model with the inclusion of a random variance component ($U_{2i}$) for WP NLE (Model 4B). Model 4B did not fit the data better for the 15WT, $\Delta\chi^2$ (3) = 4.65, $p$ = .20, however it was a better fit for MMSE, $\Delta\chi^2$ (3) = 16.17, $p$ = .001, and approached significance for Coding, $\Delta\chi^2$ (3) = 7.51, $p$ = .06. Thus, the extent to which more stress than usual affects MMSE scores and potentially Coding scores varies across people, encouraging the exploration of moderators for these outcomes.

BP NLE was not associated with the intercept or rate of decline for any of the cognitive outcomes (See Table 4, and Figure 7). WP NLE was associated with Coding, *B*[SE] = 0.27[0.09], $t(112) = 3.07$, $p < .001$, and the 15WT, *B*[SE] = 0.16[0.06], $t(122) = 2.74$, $p < .001$, in the unexpected direction (See Table 4, and Figure 8).

**Interaction between Physical Activity and Stress**

To test the interaction hypotheses, a model specifying the interaction between BP NLE and both BP PA (Model H3A; BP NLE x BP PA) and WP PA (H3B; BP NLE x WP PA), and the interaction between WP NLE and both BP PA (H4A; WP NLE x BP PA) and WP PA (H4B; WP NLE x WP PA) was fit to the data (Model 5). Specifically, this model explores the moderating effects of BP (i.e., average) and WP (i.e., occasion specific fluctuations) PA on the effects of both average stress and occasion specific stress.

Regarding Model H3A, the interaction between BP NLE and BP PA was not significant for any of the outcomes in either data set, nor was there any support for H3B, as the interaction between BP NLE and WP PA was also non-significant across study and outcomes. Therefore, the effects of average stress on cognition were not moderated by average PA level (BP PA), or occasion specific PA level (WP PA). Regarding H4A, WP NLE was not moderated by BP PA. However, in LASA WP PA positively moderated the effects of WP NLE (H4B) outcomes for Coding, *B*[SE] = 0.02[0.01], $t(1191) = 1.98$, $p = .03$, and MMSE, *B*[SE] = 0.01[0.00], $t(3407) = 2.77$, $p = .03$.

## Discussion and Limitations

The purpose of the present study was to examine the coupled association between PA and cognitive abilities, and between stress and cognitive abilities. In both the PA and stress literature, average or baseline levels of activity and stress are typically specified as predictors of cognition. However, there is reason to believe that for both predictors, there is a coupled association where fluctuation in either variable predicts fluctuations in cognitive abilities on an occasion specific basis. Additionally, the interaction between stress and PA was examined, addressing a gap in the literature regarding the relationship between stress and exercise in human populations. That is, the study intended to determine the moderating effects of BP PA and WP PA on the association between *average* stress and cognition, and on *occasion specific* stress and cognition. The present study employed specific domains of cognitive functioning (perceptual speed and episodic memory) as cognitive outcomes, in addition to a typical indicator of general decline (MMSE). Lastly, participants reported on naturally occurring life stressors, as opposed to experiencing the lab induced stressors ubiquitously examined in the cognitive literature. Analyses were conducted in two population based studies with comparable measures (MAP and LASA) for efficient reproduction.

Regarding the BP effects, it was hypothesized that higher average PA (H1A), and lower average stress (H1B) across occasions would be associated with better cognitive outcomes. For the WP effects, it was speculated that on occasions when individuals were exercising more than usual (H2A), and on occasions when individuals reported less incidence of stressors (H2B), cognitive scores would be higher. However, the effects of stress were hypothesized to be moderated by both average PA and occasion specific PA. That is, it was anticipated that the effects of average stress would be mitigated by higher average levels of PA (H4A), and on occasions when individuals were exercising more than usual (H4B), and similarly, that the

effects of occasion specific stress would be mitigated by higher average levels of PA (H5A), and on occasions when individuals were exercising more than usual (H5B).

Regarding the BP hypotheses, H1A (PA) received partial support (i.e., in MAP only), although H1B did not emerge as significant in either study. That is, in MAP, higher average PA across occasions was associated with higher average perceptual speed and episodic memory scores at baseline, and less decline in all cognitive outcomes over time (perceptual speed, episodic memory and MMSE). However, these results were not replicated in LASA. H1B, as mentioned, did not receive support in either data set, as higher average stress across occasions was not associated with the intercept or slope of any of the cognitive outcomes in either study.

Regarding the WP hypotheses, it is worth mentioning that more or less activity or stress than usual is relative to the individual. For example, a mean PA level of 13 hours per week, and a WP PA score of 1 indicates that the individual exercised 14 hours per week at that particular wave, while a participant with the same WP PA score, and a mean PA score of 3 is exercising 4 hours per week at that wave. However, this nuanced analysis allows researchers to understanding how *individuals* change as they age. Sliwinski & Buschke (2004) argue that because many hypotheses in cognitive aging pertain to individual level inferences, modeling WP change should be a more frequently adopted analytic strategy. The authors propose that the analysis of intraindividual change provides a crucial compliment to the BP analyses of correlated change, as the latter only supports inferences about how the *population* changes as it ages.

In the present study, the WP effects of PA (H2A) were supported in both MAP and LASA. That is, when individuals were exercising more than usual, they tended to score higher on all cognitive outcomes in MAP, and on the Coding task in LASA. Interestingly, H2B emerged significant in LASA in the unexpected direction, such that on occasions when individuals

reported more stressors than usual, they tended to perform better on both perceptual speed and episodic memory tasks.

The BP effects of stress (mean level across occasions), were not moderated by average PA (H3A), or by exercising more than usual at a particular occasions (H3B) in either of the data sets. In light of the nonsignificant effects of average stressors on cognition, this was somewhat expected after testing H1B. That is, an interaction between BP NLE and PA could have emerged despite the nonsignificant effects of BP NLE, however, PA could not be demonstrated to buffer against the effects of stress, as it was not negatively influencing cognitive abilities.

Additionally, the WP effects of stress were not moderated by higher average PA (H4A) in either of the studies, across all outcomes. This means that on occasions when individuals report more stressors than usual, having higher PA scores than the population average did not prove to positively influence cognitive abilities. Interestingly, H4B was supported in LASA, such that on occasions when individuals reported more stressors than usual, if they were also exercising more than usual they tended to score higher on both coding and the MMSE. In other words, when individuals experienced more stressors than usual, being less active was associated with worse cognitive performance. However, these findings should be interpreted in context. Specifically, it was expected that WP NLE would be negatively associated with cognitive scores, and PA was speculated to positively moderate this effect. However, given that the effects of both WP PA (H2A), and WP NLE (H2B) were positively related to cognitive outcomes, it seems as though the effects of WP PA on WP NLE are additive.

Discrepant findings between studies may be a function of true sample differences, such as those based on geographical location (i.e., LASA is based in the Netherlands, and MAP is based in Chicago) or other confounding variables related to location and sample, that were not included

in analyses and that would have implications for generalizability. However, certain specific differences in the predictor variables between data sets are worth noting. Firstly, In LASA, average PA was lower than in MAP, possible explaining the non-significant findings of BP PA in this sample. That is, in LASA, participants averaged 1.8 hours of activity per week; while in MAP the average hours of activity per week were 2.9. This may reflect a threshold effect, such that exercising less than, for example, 2 hours per week, does not benefit cognitive abilities, possibly explaining the unexpected non-significant findings of BP PA in LASA. Additionally, in MAP, the missing data profile of the NLE variable may have hindered the validity of the measure, accounting for the lack of significant findings at both the BP and WP level (compared to the significant findings at the WP level in LASA). For example, in MAP, dividing the number of observations for NLE by the number of unique participant ids' results in approximately 3 NLE measurements per participant, while in LASA, the average is 7. In LASA and MAP, PA was also measured on approximately 7 occasions per person. Therefore in MAP, less frequent NLE administration across waves possibly confounds both the BP and WP NLE predictor employed in the model. For example, 2 NLE assessments may not be reflective of average stress across a participant with 6 years of data, nor would a deviation from this average represent a meaningful fluctuation from "usual" levels of stress. Additionally, NLE was much more variable at the WP level (i.e. 69%, compared to 39% in LASA).

Lastly, it is possible that the present investigation was too underpowered to reveal interaction effects. In MLM, the variance of an interaction is exponentially higher than that of the main effects, requiring a large sample size for effects to emerge (Leon, Heo, 2009). The LASA analyses included 4,109 unique participants and 28,763 observations, while MAP had 1,852 participants and 11,672 observations. This may explain why in LASA, a significant

interaction between WP NLE and WP PA was found. However, future studies examining an interaction between PA and stress longitudinally would benefit from larger sample sizes.

Certain limitations regarding the PA measure in both studies should also be noted. Specifically, recall bias is inherent to self-report measures. Past research has demonstrated that the correlation between objective and self-report measures of PA range from low to moderate (Prince et al., 2008). However, in the LASA dataset, the self-report questionnaire was validated against a 7-day PA diary and a pedometer count in a subsample of 439 participants (Stel et al., 2004). Albeit, the intensity and duration of activity were not quantified in the present study, making it difficult to compare findings with past literature aiming to more precisely define PA or objectively define fitness level (e.g., measuring VO2 max). Lastly, the PA questionnaire in both studies inquired about PA levels over the past week or two, and thus may not be representative of usual levels of activity. That is, occasion specific measurements are only a snapshot of each individual in time, and may not accurately represent their true score.

Regarding stress, the present study did not support the literature demonstrating adverse effects on cognition. Higher average stress was not associated with any cognitive outcomes in either sample. Moreover, contrary to past findings, occasion specific stress predicted better cognitive performance in some instances. It is possible that the measure of stress implemented did not fit the population adequately. That is, it has been demonstrated that older adults do not necessarily experiences objective stressors, such as those listed on the NLE questionnaire, in the same way. The socioemotional selectivity theory (See Carstensen, Fung, & Charles, 2003) postulates that perceived limitations on time left lead older adults to direct their attention to emotionally meaningful goals, resulting in superior emotion regulation abilities and a tendency toward more positive emotions. This disposition likely influences the perception of negative life

events. For example, elderly participants have been demonstrated to be less reactive (i.e., experience less negative affect) to intrusive thoughts associated with daily stressors when compared to younger populations (Brose, Schmiedek, Lövdén, & Lindenberger, 2011). This underscores the importance of personal meaning, or individual perception of stress when operationalizing the construct. This is corroborated by previous findings, demonstrating that when individuals estimate the level of stress experienced as a result of the events they endorsed on the NLE, the sum of the personally weighted events (as opposed to the objective total of events experienced) were associated with overall intellectual decline and performance on a block design task (Sands, 1982). In addition to these concerns, it is arguably the case that the sources of stress for some elderly adults are more existential in nature, including personal meaning, choice/responsibility, and optimism (Reker, 1997). Thus, measuring stress with a non-exhaustive list is potentially limiting.

Additionally, the NLE questionnaire inquires about stressors since the last visit. In MAP, this was annually, and in LASA this refers to the past three years. Thus, it is difficult to disentangle proximal effects when employing this type of measure. For example, these events may indeed have a current impact, such as a recent or ongoing major illness, but in some instances they may only prove to be distally impactful with little relevance in understanding current stress. Keeping this in mind, interpretation of the positive association between WP NLE and cognitive outcomes in LASA becomes complicated. If over the past three years the participant reported more stressors that usual, it is unclear whether the stressor(s) occurred recently, almost three years ago, or at different times during the three year interval in the case of multiple stressors. Therefore, these effects could possibly represent a bounce-back effect resulting from distal stressors, or a mobilizing effect of more recent stressors.

Regarding the latter, it is well established that there is an inverted-U association between stress and cognition, such that exceptionally low or high levels of stress are associated with poorer cognitive outcomes, while moderate amounts of stress seem to optimally assist cognitive processes (Lupien & McEwen, 1997). In light of these findings, and the socioemotional selectivity theory, it is possible that if a stressor does not elicit a negative emotional response (i.e., as an exceptionally high level of perceived stress might) it may be facilitative for cognitive processes. For example, in older adults, higher daily stress has been found to be associated with a dampening in emotional-reactivity (or negative affect), and *positively* associated with fluid cognitive abilities (Stawski, Almeida, Lachman, Tun, & Rosnick, 2010). In summary, the pre-determined stressors endorsed by participants in the present study were potentially not perceived as such, possibly accounting for the positive relationship between occasion specific stress and cognition that emerged in LASA.

**Future Research**

The present study supported the hypotheses that both average PA level over time and within-person fluctuations from usual levels of activity would be predictors of cognitive performance. Given that there is minimal research examining intraindividual change in PA as a predictor of cognitive decline, future investigations would be valuable. Additionally, the present investigation did not support the hypotheses regarding the effects of stress on cognition. However, in light of the robust literature suggesting an association, null findings are likely attributable to the measure of stress employed.

In the future, a measure of stress that captures the subjective experience of the participant would be more appropriate. Given the psychological underpinning of stress, measures such as the perceived stress scale (PSS) would more adequately capture experiential stress, versus

objectively defined stress. The PSS is a measure of global stress, reflecting the extent to which an individual feels they are able to deal with the demands of their current life and how stressful they appraise their current circumstances to be. This avenue of exploration is supported by literature that implicates increasing levels of perceived stress over 6 years in impaired cognitive performance (measured by a composite score including perceptual speed, episodic memory subtests, and the MMSE) in women aged 65 and over (Aggarwal et al., 2014a). Moreover, perceived stress has been demonstrated to be associated with cerebrovascular disease (cerebral infarction and lower brain volume) in older adults (Aggarwal et al., 2014b), highlighting the importance of exploring the cognitive consequences of stress. Employing this type of measure can reduce some of the concerns regarding objectively defining stressors.

Additionally, it would be important to decipher underlying mechanisms of covariability over relatively long periods of time (e.g., years) compared to those on a shorter time scale, as the driving forces may differ (Sliwinksi, & Buschke, 2004). For example, as discussed, the effect of chronic stress on cognitive abilities has been demonstrated to be the result of neurological changes. However, on a shorter time scale, there is evidence to suggest that the effects of acute stressors on cognition are a result of cognitive interference, such that ruminative type thinking or intrusive thoughts focused on the acute stressor reduce resources allocated to the cognitive task at hand (Cohen & Spacapan, 1978; Eysenck & Calvo, 1992; Klein & Boals, 2001; Sliwinski, Smyth, Hofer, & Stawski, 2006).

In order to more accurately assess the effects of PA and stress on cognitive decline, a more involved study design would be required. Nesselroade (1991) recommends the amalgamation of two traditional longitudinal designs for understanding time dependent processes, referred to as measurement burst design (MBD). Specifically, MBD incorporates

features of short-term longitudinal daily diary studies, where measurements are taken over successive days (i.e., bursts), with more traditional longitudinal approaches, where data is collected multiple times across widely spaced intervals (i.e., the present study). Averaging stress across bursts yield a more robust representation of that person at that point in time, increasing the reliability of the predictor when compared to single measurements taken at one occasion (Sliwinki, 2008). Employing traditional longitudinal analyses using the mean of each burst to represent a participant's level of stress or PA at that particular time is less vulnerable to the variability that emerges when measuring these variables only once at a particular occasion. Moreover, an advantage of this type of design is that short-term daily diary information can be interpreted in the context of long-term developmental change. That is, at each burst, the coupled relationships between PA with cognitive abilities, and stress with cognitive abilities can be examined. Through investigating how these associations change across bursts, it would be possible to elucidate whether, with age, the association between stress and cognition, and PA and cognition change. Additionally, the mechanisms behind both long term and short-term associations, as discussed in the context of chronic and acute stress, could be determined.

Lastly, the present study did not find evidence for a protective role of PA against negative effects of stress. However, given the animal literature, and recent studies demonstrating an interaction in human populations, this is a valuable avenue for future exploration. This analyses could be included in the MBD framework, such that the interaction on a shorter time scale, and relatively longer time scale could be elucidated.

**Conclusion**

In summary, findings support the hypothesis that exercising is protective against cognitive decline. Specifically, exercising more on average and exercising more than usual both

were positively associated with cognitive outcomes. This means that in older adulthood, continuing to be physically active or transitioning from a sedentary lifestyle to a more active one can have a significant influence on cognitive abilities. Conversely, becoming less active proves to be detrimental. The present study did not support hypotheses regarding adverse effects of stress on cognitive abilities. However, in the future, it would be valuable to use a more robust measure of stress, which captures the individual's perception, and is more representative of that person at each occasion (as opposed to stress since the last visit). Moreover, it would be important to further explore the potentially positive effects of stressors on cognitive abilities in aging. Lastly, the interaction between PA and stress should continue to be explored in human populations. An intensive MBD would address some of the limitations of this investigation, and more fully paint a picture of how stress and PA are related to cognition over the lifespan.

## References

Alzheimer's Society of Canada. (2016). Prevalence and Monetary Costs of Dementia in Canada [PDF file]. Toronto. Retrieved from http://www.alzheimer.ca/~/media/Files/national/Statistics/PrevalenceandCostsofDementia_EN.pdf

Åberg, M. A., Pedersen, N. L., Torén, K., Svartengren, M., Bäckstrand, B., Johnsson, T., ... & Kuhn, H. G. (2009). Cardiovascular fitness is associated with cognition in young adulthood. *Proceedings of the National Academy of Sciences*, *106*(49), 20906-20911.

Adlard, P. A., Perreau, V. M., Engesser-Cesar, C., & Cotman, C. W. (2004). The timecourse of induction of brain-derived neurotrophic factor mRNA and protein in the rat hippocampus following voluntary exercise. *Neuroscience letters*, *363*(1), 43-48.

Aguiar, A. S., Castro, A. A., Moreira, E. L., Glaser, V., Santos, A. R., Tasca, C. I., ... & Prediger, R. D. (2011). Short bouts of mild-intensity physical exercise improve spatial learning and memory in aging rats: involvement of hippocampal plasticity via AKT, CREB and BDNF signaling. *Mechanisms of ageing and development*, *132*(11), 560-567.

Angevaren, M., Vanhees, L., Wendel-Vos, W., Verhaar, H. J., Aufdemkampe, G., Aleman, A., & Verschuren, W. M. (2007). Intensity, but not duration, of physical activities is related to cognitive function. *European Journal of Cardiovascular Prevention & Rehabilitation*, *14*(6), 825-830.

Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*, *10*(6), 410-422.

Baumgart, M., Snyder, H. M., Carrillo, M. C., Fazio, S., Kim, H., & Johns, H. (2015). Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimer's & Dementia*, *11*(6), 718-726.

Beckwith, B. E., Petros, T. V., Scaglione, C., & Nelson, J. (1986). Dose-dependent effects of hydrocortisone on memory in human males. *Physiology & behavior*, *36*(2), 283-286.

Bennett, D. A., Schneider, J. A., Buchman, A. S., Mendes de Leon, C., Bienias, J. L., & Wilson, R. S. (2005). The Rush Memory and Aging Project: study design and baseline characteristics of the study cohort. *Neuroepidemiology*, *25*(4), 163-175.

Berchtold, N. C., Chinn, G., Chou, M., Kesslak, J. P., & Cotman, C. W. (2005). Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. *Neuroscience*, *133*(3), 853-861.

Bherer, L., Erickson, K. I., & Liu-Ambrose, T. (2013). A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. *Journal of aging research*, *2013*, 1-8.Buchman, A. S., Boyle, P. A., Yu, L., Shah, R. C., Wilson, R. S., & Bennett, D. A. (2012). Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology*, *78*(17), 1323-1329.

Blondell, S. J., Hammersley-Mather, R., & Veerman, J. L. (2014). Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. *BMC public health*, *14*(1), 510.

Brose, A., Schmiedek, F., Lövdén, M., & Lindenberger, U. (2011). Normal aging dampens the link between intrusive thoughts and negative affect in reaction to daily stressors. *Psychology and aging*, *26*(2), 488.

Carstensen, L. L., Fung, H. H., & Charles, S. T. (2003). Socioemotional selectivity theory and the regulation of emotion in the second half of life. *Motivation and emotion*, *27*(2), 103-123.

Cerqueira, J. J., Mailliet, F., Almeida, O. F., Jay, T. M., & Sousa, N. (2007). The prefrontal cortex as a key target of the maladaptive response to stress. *Journal of Neuroscience*, *27*(11), 2781-2787.

Chang, M., Jonsson, P. V., Snaedal, J., Bjornsson, S., Saczynski, J. S., Aspelund, T., ... & Gudnason, V. (2010). The effect of midlife physical activity on cognitive function among older adults: AGES—Reykjavik Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *65*(12), 1369-1374.

Chasteen, A. L., Bhattacharyya, S., Horhota, M., Tam, R., & Hasher, L. (2005). How feelings of stereotype threat influence older adults' memory performance. *Experimental aging research*, *31*(3), 235-260.

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., ... & Kramer, A. F. (2006). Aerobic exercise training increases brain volume in aging humans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *61*(11), 1166-1170.

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychological science*, *14*(2), 125-130.

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., ... & Elavsky, S. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National academy of Sciences of the United States of America*, *101*(9), 3316-3321.

Crews, D. J., & Landers, D. M. (1987). A meta-analytic review of aerobic fitness and reactivity to psychosocial stressors. *Medicine and science in sports and exercise*, *19*(5 Suppl), S114-20.

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., ... & Wojcicki, T. R. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences*, *108*(7), 3017-3022.

Erickson, K. I., Weinstein, A. M., & Lopez, O. L. (2012). Physical activity, brain plasticity, and Alzheimer's disease. *Archives of medical research*, *43*(8), 615-621.

Ferris, L. T., Williams, J. S., & Shen, C. L. (2007). The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Medicine and science in sports and exercise*, *39*(4), 728.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*, *12*(3), 189-198.

Griffin, É. W., Mullally, S., Foley, C., Warmington, S. A., O'Mara, S. M., & Kelly, Á. M. (2011). Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiology & behavior*, *104*(5), 934-941.

Hamer, M. (2012). Psychosocial stress and cardiovascular disease risk: the role of physical activity. *Psychosomatic Medicine*, *74*(9), 896-903.

Hamer, M., & Chida, Y. (2009). Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychological medicine*, *39*(01), 3-11.

Hamer, M., Sabia, S., Batty, G. D., Shipley, M. J., Tabák, A. G., Singh-Manoux, A., & Kivimaki, M. (2012). Physical activity and inflammatory markers over 10 years: follow-up in men and women from the Whitehall II cohort study. *Circulation*, CIRCULATIONAHA-112.

Hamer, M., Taylor, A., & Steptoe, A. (2006). The effect of acute aerobic exercise on stress related blood pressure responses: a systematic review and meta-analysis. *Biological psychology*, *71*(2), 183-190.

Harada, C. N., Love, M. C. N., & Triebel, K. L. (2013). Normal cognitive aging. *Clinics in geriatric medicine*, *29*(4), 737-752.

Head, D., Singh, T., & Bugg, J. M. (2012). The moderating role of exercise on stress-related effects on the hippocampus and memory in later adulthood. *Neuropsychology*, *26*(2), 133.

Heaney, J. L., Carroll, D., & Phillips, A. C. (2014). Physical activity, life events stress, cortisol, and DHEA: preliminary findings that physical activity may buffer against the negative effects of stress. *Journal of aging and physical activity*, *22*(4), 465-473.

Hofer, S. M., & Piccinin, A. M. (2009). Integrative data analysis through coordination of measurement and analysis protocol across independent longitudinal studies. *Psychological methods*, *14*(2), 150.

Hoffman, L. (2015). *Longitudinal analysis: Modeling within-person fluctuation and change*. Routledge: Taylor and Francis Group, New York and London.

Huisman, M., Poppelaars, J., van der Horst, M., Beekman, A. T., Brug, J., van Tilburg, T. G., & Deeg, D. J. (2011). Cohort profile: the longitudinal aging study Amsterdam. *International journal of epidemiology*, dyq219.

Karr, J. E., Areshenkoff, C. N., Rast, P., & Garcia-Barrera, M. A. (2014). An empirical comparison of the therapeutic benefits of physical exercise and cognitive training on the executive functions of older adults: A meta-analysis of controlled trials. *Neuropsychology*, *28*(6), 829.

Knaepen, K., Goekint, M., Heyman, E. M., & Meeusen, R. (2010). Neuroplasticity—exercise-induced response of peripheral brain-derived neurotrophic factor. *Sports medicine*, *40*(9), 765-801.

Kramer, A. F., Colcombe, S. J., Erickson, K. I., & Paige, P. (2006, April). Fitness training and the brain: From molecules to minds. In *Proceedings of the 2006 Cognitive Aging Conference, Atlanta, Georgia*.

Kramer, A. F., & Erickson, K. I. (2007). Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. *Trends in cognitive sciences*, *11*(8), 342-348.

Kwon, D. H., Kim, B. S., Chang, H., Kim, Y. I., Jo, S. A., & Leem, Y. H. (2013). Exercise ameliorates cognition impairment due to restraint stress-induced oxidative insult and reduced BDNF level. *Biochemical and biophysical research communications*, *434*(2), 245-251.

Leon, A. C., & Heo, M. (2009). Sample sizes required to detect interactions between two binary fixed-effects in a mixed-effects linear regression model. *Computational statistics & data analysis*, *53*(3), 603-608.

Lindwall, M., Cimino, C. R., Gibbons, L. E., Mitchell, M. B., Benitez, A., Brown, C. L., ... & MacDonald, S. W. (2012). Dynamic associations of change in physical activity and change in cognitive function: coordinated analyses of four longitudinal studies. *Journal of Aging Research*, *2012*.

Lommatzsch, M., Zingler, D., Schuhbaeck, K., Schloetcke, K., Zingler, C., Schuff-Werner, P., & Virchow, J. C. (2005). The impact of age, weight and gender on BDNF levels in human platelets and plasma. *Neurobiology of aging*, *26*(1), 115-123.

Liu, D., Zhang, Q., Gu, J., Wang, X., Xie, K., Xian, X., ... & Wang, Z. (2014). Resveratrol prevents impaired cognition induced by chronic unpredictable mild stress in rats. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *49*, 21-29.

Lupien, S., Lecours, A., Schwartz, G., Sharma, S., Hauger, R. L., Meaney, M. J., & Nair, N. P. V. (1996). Longitudinal study of basal cortisol levels in healthy elderly subjects: evidence for subgroups. *Neurobiology of Aging*, *17*(1), 95-105.

Lupien, S. J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T. E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and cognition*, *65*(3), 209-237.

Lupien, S. J., & McEwen, B. S. (1997). The acute effects of corticosteroids on cognition: integration of animal and human model studies. *Brain Research Reviews*, *24*(1), 1-27.

Lytle, M. E., Vander Bilt, J., Pandav, R. S., Dodge, H. H., & Ganguli, M. (2004). Exercise level and cognitive decline: the MoVIES project. *Alzheimer Disease & Associated Disorders*, *18*(2), 57-64.

McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*(1), 33-44.

McEwen, B. S., & Morrison, J. H. (2013). The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron*, *79*(1), 16-29.

McEwen, B. S., & Stellar, E. (1993). Stress and the individual: mechanisms leading to disease. *Archives of internal medicine*, *153*(18), 2093-2101.

Middleton, L. E., Barnes, D. E., Lui, L. Y., & Yaffe, K. (2010). Physical activity over the life course and its association with cognitive performance and impairment in old age. *Journal of the American Geriatrics Society*, *58*(7), 1322-1326.

Miller, D. I., Taler, V., Davidson, P. S., & Messier, C. (2012). Measuring the impact of exercise on cognitive aging: methodological issues. *Neurobiology of aging*, *33*(3), 622-e29.

Moms, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., Van Belle, G., Fillenbaum, G. D. M. E., ... & Clark, C. (1989). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assesment of Alzheimer's disease. *Neurology*, *39*(9), 1159-1159.

Nation, D. A., Hong, S., Jak, A. J., Delano-Wood, L., Mills, P. J., Bondi, M. W., & Dimsdale, J. E. (2011). Stress, exercise, and Alzheimer's disease: A neurovascular pathway. *Medical hypotheses*, *76*(6), 847-854.

Neupert, S. D., Almeida, D. M., Mroczek, D. K., & Spiro III, A. (2006). Daily stressors and memory failures in a naturalistic setting: findings from the VA Normative Aging Study. *Psychology and aging*, *21*(2), 424.

Newcomer, J. W., Selke, G., Melson, A. K., Hershey, T., Craft, S., Richards, K., & Alderson, A. L. (1999). Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Archives of general psychiatry*, *56*(6), 527-533.

Pedersen BK. Exercise-induced myokines and their role in chronic diseases. Brain Behav Immun 2011; 25: 811–6.

Piccinin, A. M., Muniz, G., Sparks, C., & Bontempo, D. E. (2011). An evaluation of analytical approaches for understanding change in cognition in the context of aging and health. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *66*(suppl 1), i36-i49.

Podewils, L. J., Guallar, E., Kuller, L. H., Fried, L. P., Lopez, O. L., Carlson, M., & Lyketsos, C. G. (2005). Physical activity, APOE genotype, and dementia risk: findings from the

Cardiovascular Health Cognition Study. *American journal of epidemiology*, *161*(7), 639-651.

Prince, S. A., Adamo, K. B., Hamel, M. E., Hardt, J., Gorber, S. C., & Tremblay, M. (2008). A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. *International Journal of Behavioral Nutrition and Physical Activity*, *5*(1), 56.

Reker, G. T. (1997). Personal meaning, optimism, and choice: Existential predictors of depression in community and institutional elderly. *The Gerontologist*, *37*(6), 709-716.

Rosnick, C. B., Small, B. J., Borenstein Graves, A., & Mortimer, J. A. (2004). Health predictors of cognition in the Charlotte County Healthy Aging Study. *Aging, Neuropsychology and Cognition*, *11*, 89-99.

Rothman, S. M., & Mattson, M. P. (2013). Activity-dependent, stress-responsive BDNF signaling and the quest for optimal brain health and resilience throughout the lifespan. *Neuroscience*, *239*, 228-240.

Salthouse, T. A. (2000). Aging and measures of processing speed. *Biological psychology*, *54*(1), 35-54.

Sothmann, M. S., Buckworth, J., Claytor, R. P., Cox, R. H., White-Welkley, J. E., & Dishman, R. K. (1996). Exercise training and the cross-stressor adaptation hypothesis. *Exercise and sport sciences reviews*, *24*(1), 267-288.

Tsatsoulis, A., & Fountoulakis, S. (2006). The protective role of exercise on stress system dysregulation and comorbidities. *Annals of the New York Academy of Sciences*, *1083*(1), 196-213.

Saczynski, J. S., Rebok, G. W., & Holtzman, R. E. (2002). Stressful life events and cognitive functioning in mid and late life. In *55th Annual Scientific Meeting of the Gerontological Society of America, Boston, MA*.

Sands, J. D. (1982). The relationship of stressful life events to intellectual functioning in women over 65. *The International Journal of Aging and Human Development*, *14*(1), 11-22.

Sapolsky, R. M., Krey, L. C., & McEWEN, B. S. (1986). The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocrine reviews*, *7*(3), 284-301.

Savage, R. D. (1984). Alphabet Coding task-15. *Unpublished manuscript, Murdoch University, Perth, Western Australia*.

Seeman, T. E., McEwen, B. S., Singer, B. H., Albert, M. S., & Rowe, J. W. (1997b). Increase in urinary cortisol excretion and memory declines: MacArthur Studies of successful aging 1. *The Journal of Clinical Endocrinology & Metabolism*, *82*(8), 2458-2465.

Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I., & McEwen, B. S. (1997a). Price of adaptation—allostatic load and its health consequences: MacArthur studies of successful aging. *Archives of internal medicine*, *157*(19), 2259-2268.

Singer, J. D., & Willet, J. B. (2003). A framework for investigating change over time. *Applied longitudinal data analysis: Modeling change and event occurrence*, 3-15.

Sliwinski, M. J., Smyth, J. M., Hofer, S. M., & Stawski, R. S. (2006). Intraindividual coupling of daily stress and cognition. *Psychology and aging*, *21*(3), 545.

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., & Macchi, C. (2011). Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *Journal of internal medicine*, *269*(1), 107-117.

Stawski, R. S., Almeida, D. M., Lachman, M. E., Tun, P. A., & Rosnick, C. B. (2010). Fluid cognitive ability is associated with greater exposure and smaller reactions to daily stressors. *Psychology and aging*, *25*(2), 330.

Stel, V. S., Smit, J. H., Pluijm, S. M., Visser, M., Deeg, D. J., & Lips, P. (2004). Comparison of the LASA Physical Activity Questionnaire with a 7-day diary and pedometer. *Journal of clinical epidemiology*, *57*(3), 252-258.

Traustadóttir, T., Bosch, P. R., & Matt, K. S. (2005). The HPA axis response to stress in women: effects of aging and fitness. *Psychoneuroendocrinology*, *30*(4), 392-402.

Weschler, D. (1987). Weschler memory scale-Revised. *San Antonio: The Psychological Corporation*.

Yaffe, K., Barnes, D., Nevitt, M., Lui, L. Y., & Covinsky, K. (2001). A prospective study of physical activity and cognitive decline in elderly women: women who walk. *Archives of internal medicine*, *161*(14), 1703-1708.

Table 1

*Model 1 Parameter Estimates for all Cognitive Outcomes in MAP and LASA*

| | Perceptual Speed | | Episodic Memory | | MMSE | |
|---|---|---|---|---|---|---|
| | *MAP* | *LASA* | *MAP* | *LASA* | *MAP* | *LASA* |
| | *B(SE)* | *B(SE)* | *B(SE)* | *B(SE)* | *B(SE)* | *B(SE)* |
| Fixed Effects | | | | | | |
| (Intercept) | 37.36(.28)*** | 29.44(.42)*** | 17.20(.11)*** | 9.99(.16)*** | 27.83(.08)*** | 28.67(.07)*** |
| Time | -1.35(.05)*** | -1.08(.05)*** | -0.24(.02)*** | -0.33(.03)*** | -0.66(.03)*** | -0.21(.02)*** |
| Within-person random Effects | | | | | | |
| $\sigma^2$ (Residual) | 28.62 | 6.642 | 7.00 | 2.736 | 4.598 | 2.205 |
| Between-person random effects | | | | | | |
| $\tau_{00}$ (Intercept) | 125.34 | 33.127 | 18.274 | 3.013 | 9.752 | 0.960 |
| $\tau_{01}$ (Time Slope) | 1.613 | 0.347 | 0.278 | 0.045 | 0.861 | 0.105 |
| $N_{id}$ | 1816 | 219 | 1843 | 219 | 1848 | 550 |
| $N_{observations}$ | 10591 | 1485 | 10976 | 1299 | 11324 | 3848 |

*Note. B* = parameter estimate; *SE* = standard error; perceptual speed was measured with the SDMT in MAP, and Coding task in LASA; episodic memory was measured with the WLI in MAP and 15WT in LASA; *$p$ < .05, **$p$ <.01, ***$p$ <.001

Table 2

*Model 2 Parameter Estimates for all Cognitive Outcomes in MAP and LASA*

| | Perceptual Speed | | Episodic Memory | | MMSE | |
|---|---|---|---|---|---|---|
| | *MAP* | *LASA* | *MAP* | *LASA* | *MAP* | *LASA* |
| | *B(SE)* | *B(SE)* | *B(SE)* | B(*SE*) | *B(SE)* | *B(SE)* |
| Fixed Effects | | | | | | |
| (Intercept) | 38.62(.29)*** | 30.19(.51)*** | 18.01(.011)*** | 10.62(.20)*** | 28.28(.09)*** | 28.82(.11)*** |
| Time | -1.33(.05)*** | -1.10(.07)*** | -0.26(.02)*** | -0.37(.04) *** | -0.65(.03)*** | -0.31(.03)*** |
| Age BL | -0.50(.03)*** | -0.24(.09)** | -0.18(.01)*** | -0.05(.03) | -0.08(.01)*** | 0.03(.01)* |
| Sex | -3.05(.57)*** | -2.51(.81)** | -2.34(.22)*** | -1.64(.31)*** | -1.36(.18)*** | -0.15(.14) |
| Education | 1.04(.08)*** | 0.73(.13)*** | 0.36(.03)*** | 0.14(.05)** | 0.18(.02)*** | 0.09(.02)*** |
| Time x Age BL | -0.08(.01)*** | -0.04(.01)** | -0.02(.00)*** | -0.01(.01) | -0.04(.00)*** | -0.02(.00)*** |
| Time x Sex | 0.03(.10) | -0.04(.11) | 0.09(.04)* | 0.07(.06) | 0.02(.06) | -0.04(.04) |
| Time x Education | 0.00(.01) | -0.03(.02) | -0.00(.01) | -0.01(.01) | 0.01(.01) | 0.02(.01)** |
| Within-person random effects | | | | | | |
| $\sigma^2_{(Residual)}$ | 28.715 | 6.634 | 7.013 | 2.735 | 4.608 | 2.205 |
| Between-person random effects | | | | | | |
| $\tau_{00\ (Intercept)}$ | 98.290 | 26.776 | 14.041 | 2.340 | 8.690 | 0.871 |
| $\tau_{01\ (Time\ Slope)}$ | 1.24 | 0.321 | 0.248 | 0.042 | 0.759 | 0.087 |
| $N_{id}$ | 1816 | 219 | 1843 | 219 | 1848 | 550 |
| $N_{Observations}$ | 10591 | 1485 | 10976 | 1299 | 11324 | 3848 |

*Note. B* = parameter estimate; *SE* = standard error; Age BL = age at baseline; female is the reference group; Age BL and Education were centered upon the population mean; perceptual speed was measured with the SDMT in MAP, and Coding task in LASA; episodic memory was measured with the WLI in MAP and 15WT in LASA

Table 3

*Model 3B Parameter Estimates for all Cognitive Outcomes in MAP and LASA*

| | Perceptual Speed | | Episodic Memory | | MMSE | |
|---|---|---|---|---|---|---|
| | *MAP* | *LASA* | *MAP* | *LASA* | *MAP* | *LASA* |
| | *B(SE)* | *B(SE)* | *B(SE)* | *B(SE)* | *B(SE)* | *B(SE)* |
| Fixed Effects | | | | | | |
| (Intercept) | 38.58(.29)*** | 30.16(.61)*** | 18.00(.11)*** | 10.66(.23)*** | 28.22(.09)*** | 28.80(.12)*** |
| Time | -1.24(.05)*** | -1.10(.08)*** | -0.23(.02)*** | -0.35(.05)*** | -0.59(.03)*** | -0.30(.03)*** |
| Age BL | -0.49(.03)*** | -0.25(.09)** | -0.18(.01)*** | -0.05(.04) | -0.08(.01) *** | 0.02(.01)* |
| Sex | -3.09(.57)*** | -2.53(.87)** | -2.35(.22) *** | -1.67(.34)*** | -1.35(.17)*** | -0.13(.14) |
| Education | 1.01(.08)*** | 0.73(.13)*** | 0.34 (.03)** | 0.14(.05)** | 0.17(.02)*** | 0.09(.02)*** |
| PA BP | 0.23(.09)* | -0.02(.09) | 0.10(.04)** | -0.01(.04) | 0.05(.03). | -0.01(.02) |
| Time x Age BL | -0.07(.01)*** | -0.03(.01)** | -0.02(.00)*** | -0.01(.01) | -0.03(.00)*** | -0.02(.00)*** |
| Time x Sex | -0.06(.09) | -0.03(.12) | 0.06(.04) | 0.10(.07) | 0.00(.06) | -0.05(.04) |
| Time x Education | -0.00(.01) | -0.03(.02) | -0.00(.01) | -0.01(.01) | 0.01(.01) | 0.01(.01)** |
| Time x PA BP | 0.06(.02)*** | 0.01(.01) | 0.03(.01)*** | -0.00(.01) | 0.04(.01)*** | 0.00(.00) |
| PA WP | 0.06(.02)* | 0.03(.01)* | 0.03(.01)* | 0.01(.01) | 0.03(.01)* | 0.01(.00) |
| Within-person random effects | | | | | | |
| $\sigma^2_{(Residual)}$ | 28.268 | 6.610 | 6.897 | 2.694 | 4.184 | 2.190 |
| Between-person random effects | | | | | | |
| $\tau_{00\ (Intercept)}$ | 96.450 | 26.504 | 13.665 | 2.148 | 8.381 | 0.744 |
| $\tau_{01\ (Time\ Slope)}$ | 1.063 | 0.308 | 0.221 | 0.038 | 0.605 | 0.070 |
| $\tau_{02\ (PA\ WP)}$ | 0.022 | 0.000 | 0.011 | 0.001 | 0.011 | 0.000 |
| $N_{id}$ | 1814 | 219 | 1840 | 219 | 1846 | 550 |
| $N_{Observations}$ | 10466 | 1485 | 10834 | 1299 | 11074 | 3848 |

*Note. B* = parameter estimate; *SE* = standard error; Age BL = age at baseline; female is the reference group; Age BL, Education, and PA BP were centered upon the population mean; PA WP represent occasion specific scores centered upon individuals unique PA means; perceptual speed was measured with the SDMT in MAP, and Coding task in LASA; episodic memory was measured with the WLI in MAP and 15WT in LASA; *$p$ < .05, **$p$ <.01, ***$p$ <.001

Table 4
*Model 4B Parameter Estimates for all Cognitive Outcomes in MAP and LASA*

| | Perceptual Speed | | Episodic Memory | | MMSE | |
|---|---|---|---|---|---|---|
| | *MAP* | *LASA* | *MAP* | *LASA* | *MAP* | *LASA* |
| | *B(SE)* | *B(SE)* | *B(SE)* | *B(SE)* | *B(SE)* | *B(SE)* |
| Fixed Effects | | | | | | |
| (Intercept) | 41.55(.42) *** | 30.28(1.02)*** | 19.19(.19)*** | 10.48(.39)*** | 28.66(.12)*** | 28.76(.19)*** |
| Time | -0.99(.07)*** | -1.25(.14)*** | -0.15(.03)*** | -0.40(.08)*** | -0.27(.03)*** | -0.31(.05)*** |
| Age BL | -0.43(.05)*** | -0.24(.09)** | -0.19(.02)*** | -0.04(.03) | -0.07(.01)*** | 0.02(.01) |
| Sex | -1.98(.87)* | -2.51(.85)** | -2.80(.39)*** | -1.56(.33)*** | -0.79(.25)** | -0.13(.15) |
| Education | 0.78(.13)*** | 0.70(.13)*** | 0.32(.06)*** | 0.13(.05)** | 0.10(.04)* | 0.09(.02)*** |
| NLE BP | -0.43(.25) | 0.07(.69) | 0.09(.11) | 0.21(.27) | 0.09(.07) | 0.06(.12) |
| Time x Age BL | -0.06(0.01) | -0.04(.01)** | -0.01(.00)* | -0.01(.01) | -0.01(.00)*** | -0.02(.00)*** |
| Time x Sex | -0.09(.13) | 0.00(.11) | 0.08(.07) | 0.08(.07) | 0.01(.05) | -0.04(.04) |
| Time x Education | -0.29(.02) | -0.02(.02) | -0.01(.01) | -0.01(.01) | 0.00(.01) | 0.01(.01)** |
| Time x NLE BP | -0.04(.04) | 0.08(.09) | -0.03(.02) | -0.01(.05) | -0.01(.16) | 0.00(.03) |
| NLE WP | -0.15(0.08) | 0.27(.09)** | 0.01(.04) | 0.16(.06)** | 0.01(.02) | 0.05(.03) |
| Within-person random effects | | | | | | |
| $\sigma^2_{(Residual)}$ | 26.300 | 6.302 | 6.634 | 2.606 | 1.935 | 2.189 |
| Between-person random effects | | | | | | |
| $\tau_{00\ (Intercept)}$ | 75.301 | 28.149 | 12.699 | 2.462 | 5.558 | 0.918 |
| $\tau_{01\ (Time\ Slope)}$ | 0.489 | 0.358 | 0.141 | 0.038 | 0.173 | 0.096 |
| $\tau_{02\ (NLE\ WP)}$ | 0.246 | 0.295 | 0.020 | 0.111 | 0.028 | 0.018 |
| $N_{id}$ | 988 | 219 | 1003 | 219 | 1001 | 550 |
| $N_{Observations}$ | 3220 | 1485 | 3309 | 1299 | 3293 | 3848 |

*Note. B* = parameter estimate; *SE* = standard error; Age BL = age at baseline; female is the reference group; Age BL, Education, and NLE BP were centered upon the population mean; NLE WP represent occasion specific scores centered upon individuals unique PA means; perceptual speed was measured with the SDMT in MAP, and Coding task in LASA; episodic memory was measured with the WLI in MAP and 15WT in LASA; *$p$ < .05, **$p$ <.01, ***$p$ <.001

*Table 5*
*Model 5 Parameter Estimates for all Cognitive Outcomes in MAP and LASA*

| | Perceptual Speed | | Episodic Memory | | MMSE | |
|---|---|---|---|---|---|---|
| | *MAP* | *LASA* | *MAP* | *LASA* | *MAP* | *LASA* |
| Fixed Effects | | | | | | |
| (Intercept) | 41.51(.43)*** | 30.12(1.18)*** | 19.14(.19)*** | 10.69(.41)*** | 28.63(.12)*** | 28.70(.20)*** |
| Time | -0.99(.07)*** | -1.12(.07)*** | -0.14(.03)*** | -0.40(.04)*** | -0.26(.02) *** | -0.30(.03)*** |
| Age BL | -0.41(.05)*** | -0.24(.09)** | -0.18(.02)*** | -0.05(.03) | -0.07(.01)*** | 0.02(.01)* |
| Sex | -2.02(.88)* | -2.49(.88)** | -2.83(.39)*** | -1.52(.33)*** | -0.81(.25)** | -0.16(.15) |
| Education | 0.77(.13)*** | 0.70(.13)*** | 0.31(.06)*** | 0.13(.05)** | 0.09(.04)* | 0.09(.02)*** |
| NLE BP | -0.54(.22)* | 0.03(.84) | 0.01(.09) | 0.08(.28) | 0.06(.06) | 0.11(.14) |
| PA BP | 0.20(.13) | -0.06(.15) | 0.11(.06)* | -0.04(.05) | 0.02(.03) | 0.01(.02) |
| PA WP | 0.06(.04) | 0.01(.02) | 0.05(.02)* | 0.00(.02) | 0.02(.01) | 0.01(.01) |
| NLE WP | -0.15(.08) | 0.29(.13)* | 0.00(.04) | 0.21(.09)* | 0.02(.02) | 0.09(.04)* |
| Time x Age BL | -0.06(.01)*** | -0.04(.01)** | -0.01(.00) * | -0.01(.01) | -0.01(.00)*** | -0.02(.00)*** |
| Time x Sex | 0.10(.13) | -0.02(.11) | 0.08(.06) | 0.08(.06) | 0.01(.05) | -0.03(.04) |
| Time x Education | -0.03(.02) | -0.02(.02) | -0.01(.01) | -0.00(.01) | 0.00(.01) | 0.01(.01)** |
| NLE BP x PA BP | -0.12(.10) | 0.07(.13) | -0.03(.04) | 0.02(.04) | -0.01(.02) | -0.01(.02) |
| NLE BP x PA WP | 0.05(.04) | 0.03(.02) | -0.02(.02) | 0.01(.01) | -0.01(.01) | -0.00(.01) |
| PA BP x NLE WP | 0.00(.03) | -0.00(.02) | 0.02(.01) | -0.01(.01) | 0.01(.01) | -0.01(.01) |
| PA WP x NLE WP | -0.02(.04) | 0.02(.01)* | -0.00(.02) | 0.01(.01) | -0.00(.01) | 0.01(.00)** |
| Within-person random effects | | | | | | |
| $\sigma^2_{(Residual)}$ | 26.243 | 6.280 | 6.628 | 2.612 | 1.939 | 2.181 |
| Between-person random effects | | | | | | |
| $\tau_{00\ (Intercept)}$ | 75.151 | 28.042 | 12.362 | 2.419 | 5.070 | 0.917 |
| $\tau_{01\ (Time\ Slope)}$ | 0.495 | 0.358 | 0.130 | 0.035 | 0.149 | 0.096 |
| $\tau_{02\ (NLE\ WP)}$ | 0.253 | 0.277 | 0.016 | 0.107 | 0.021 | 0.018 |
| $N_{id}$ | 986 | 219 | 999 | 219 | 999 | 550 |
| $N_{Observations}$ | 3214 | 1485 | 3285 | 1299 | 3296 | 3848 |

*Note. B* = parameter estimate; *SE* = standard error; Age BL = age at baseline; female is the reference group; Age BL, Education, PA_BP, and NLE BP were centered upon the respective population means; NLE WP and PA WP represent occasion specific scores centered upon individuals unique NLE means, and PA means, respectively; perceptual speed was measured with the SDMT in MAP, and Coding task in LASA; episodic memory was measured with the WLI in MAP and 15WT in LASA; *$p$ < .05, **$p$ <.01, ***$p$ <.001

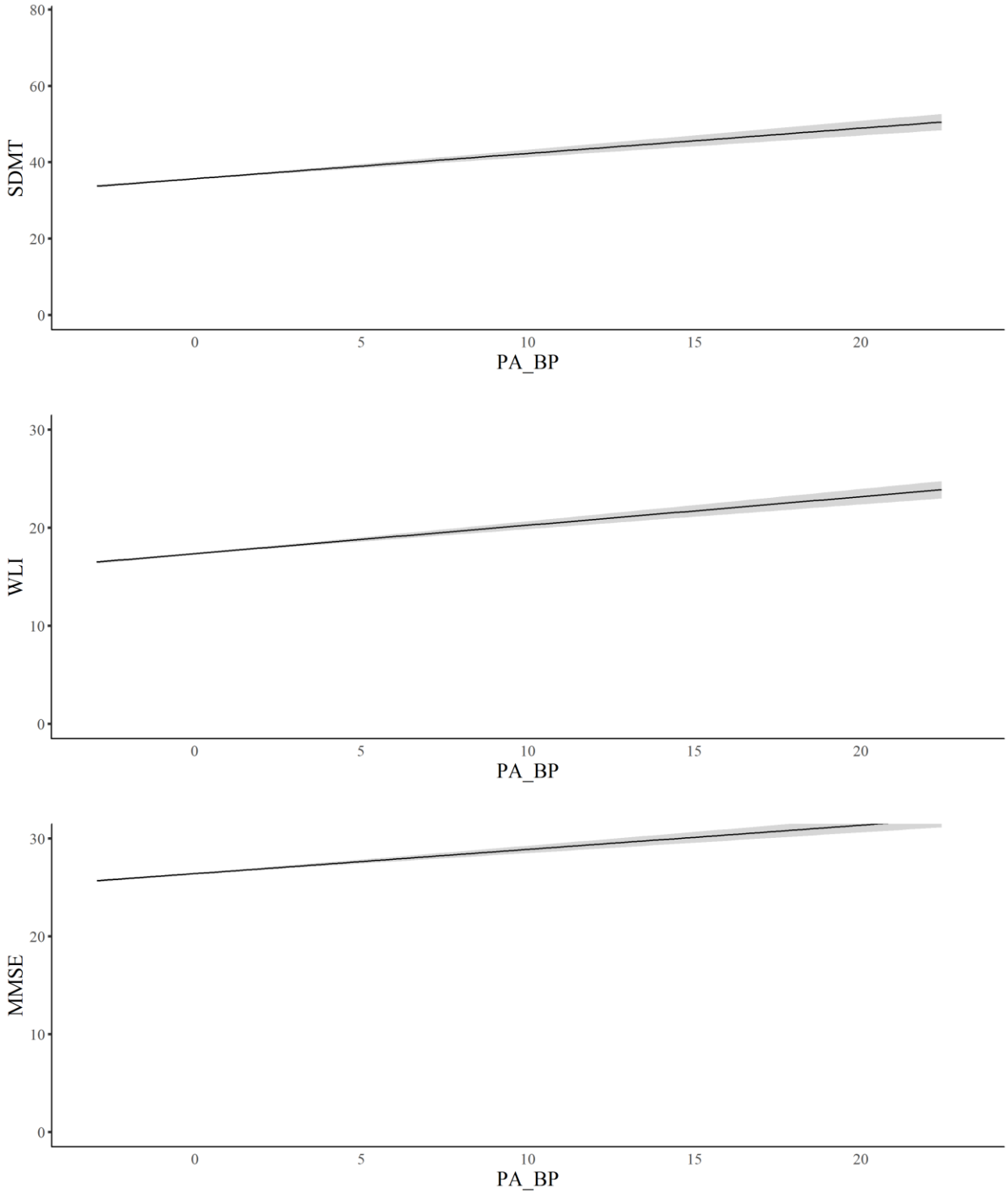


*Figure 1*. Between-Person Effects of PA on SDMT, WLI, and the MMSE in MAP

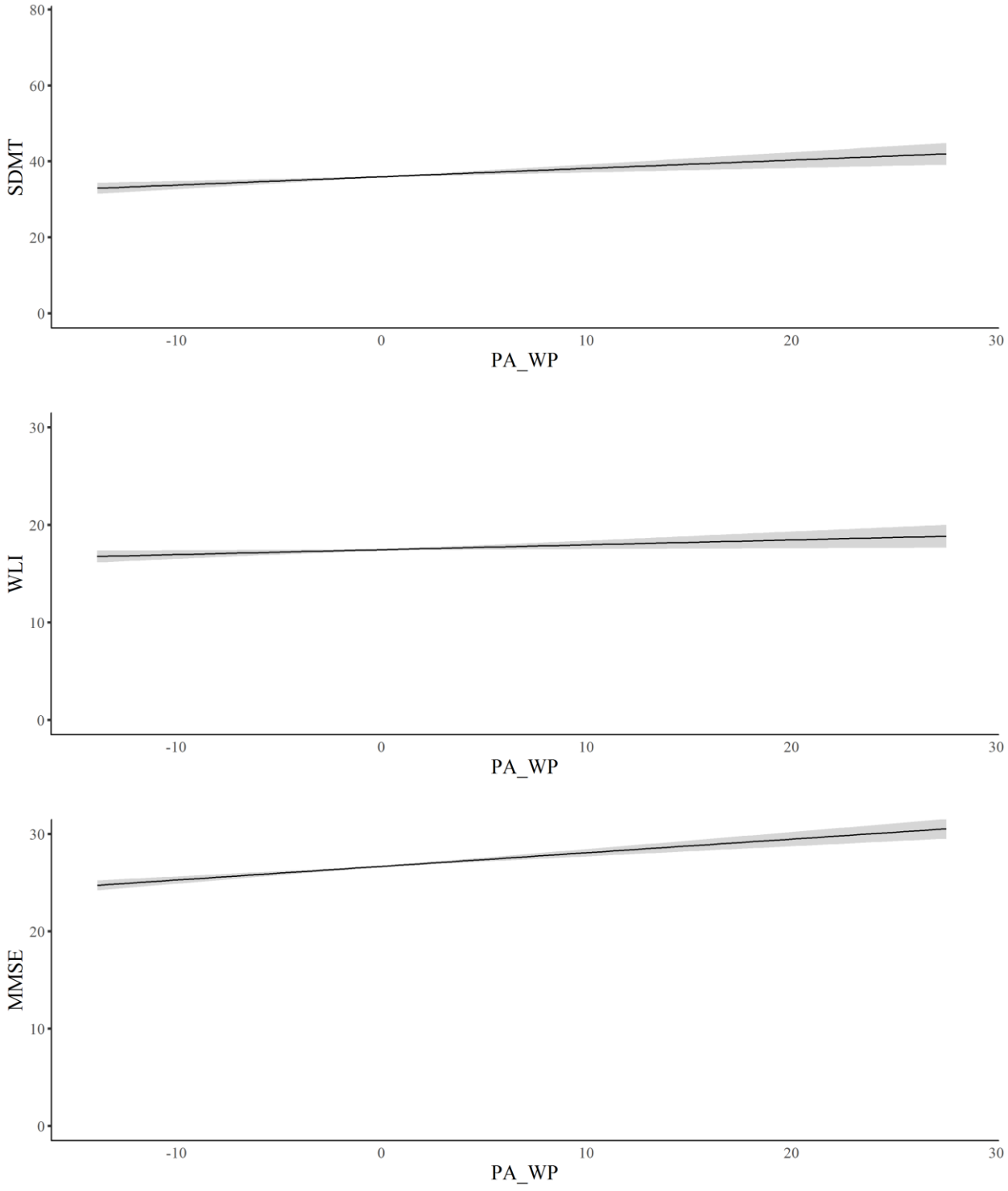


*Figure 2*. Within-Person Effects of PA on SDMT, WLI, and the MMSE in MAP

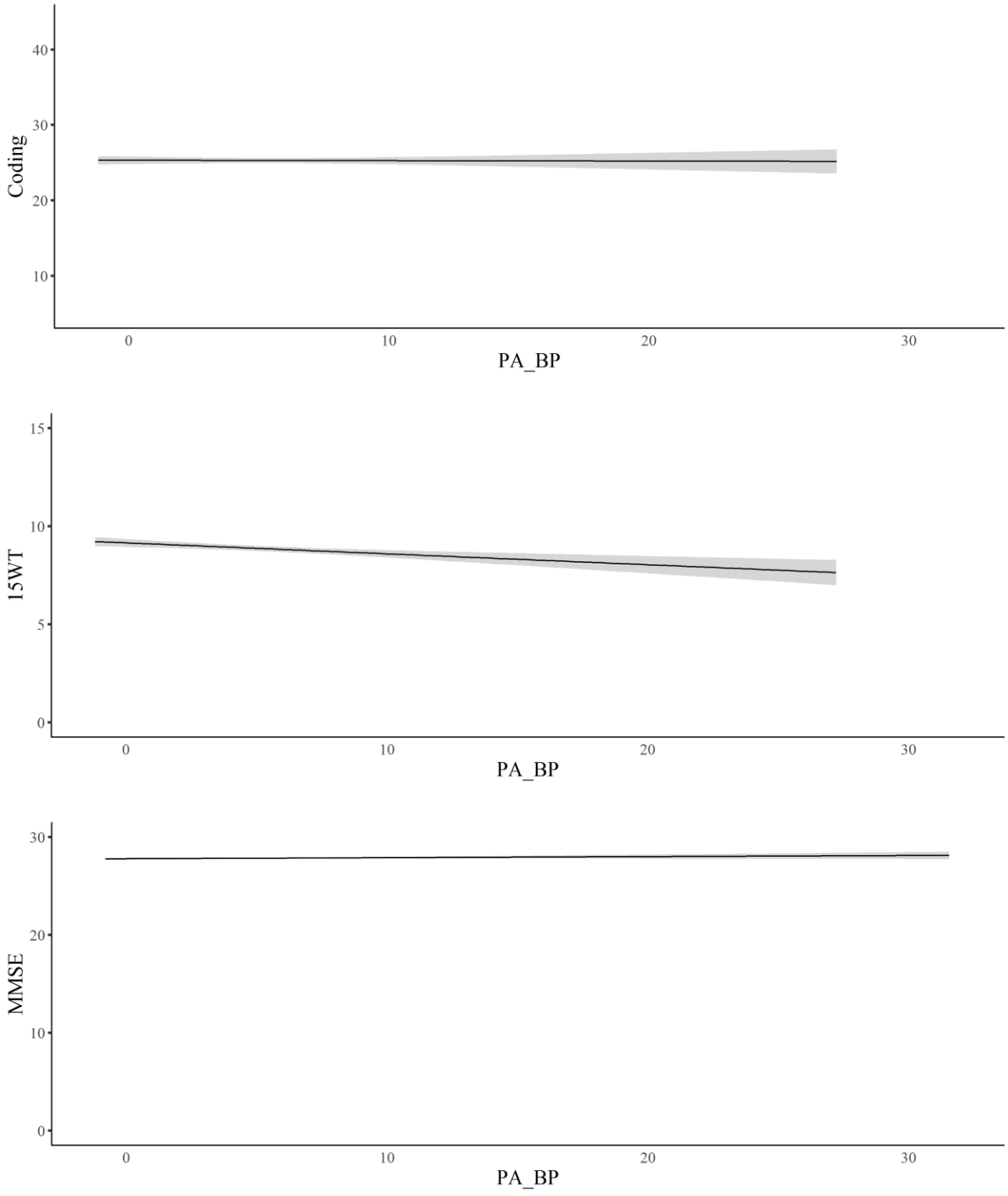


*Figure 3*. Between-Person Effects of PA on Coding, 15WT, and MMSE in LASA

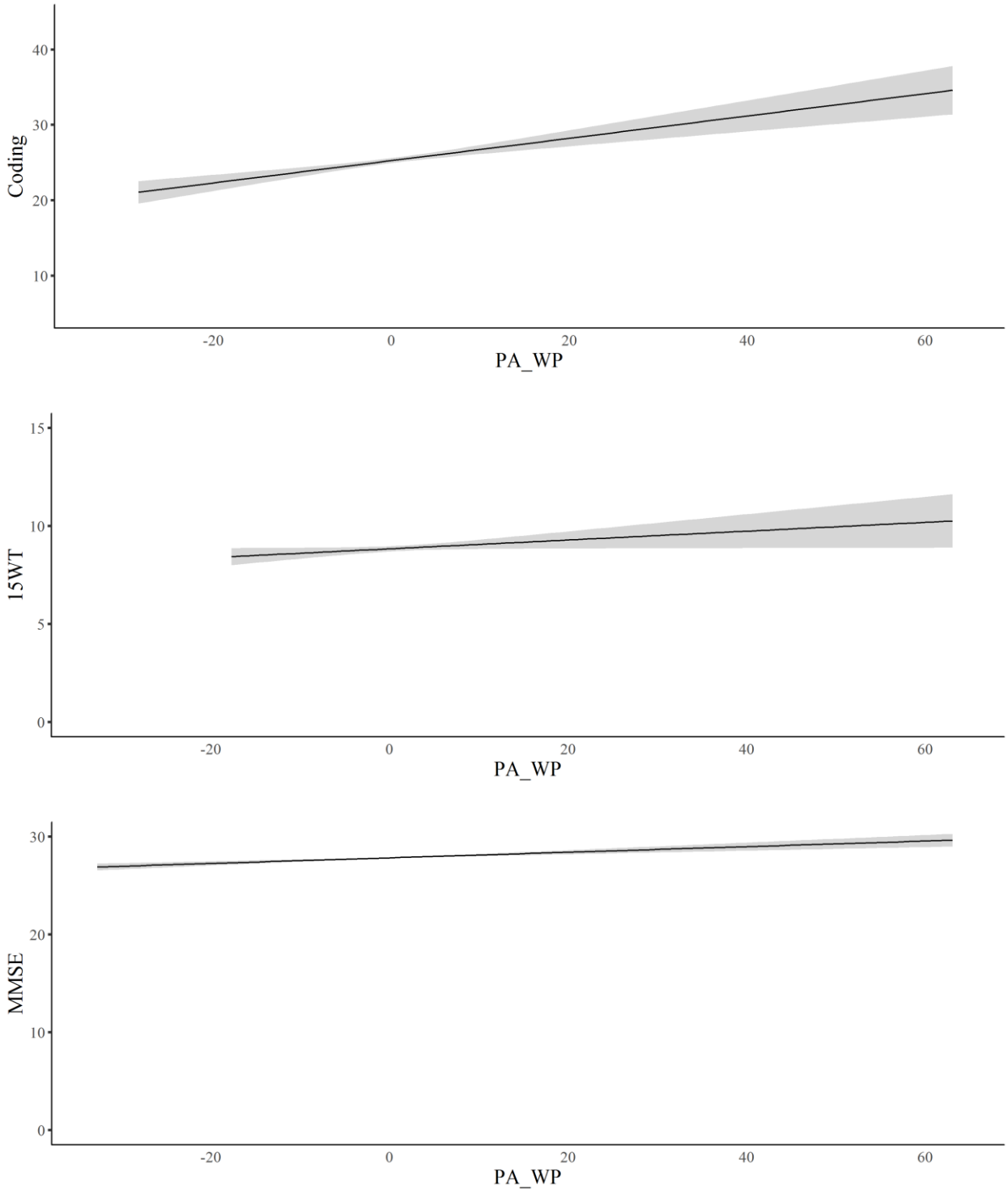


*Figure 4*: Within-Person Effects of PA on Coding, 15WT and MMSE in LASA

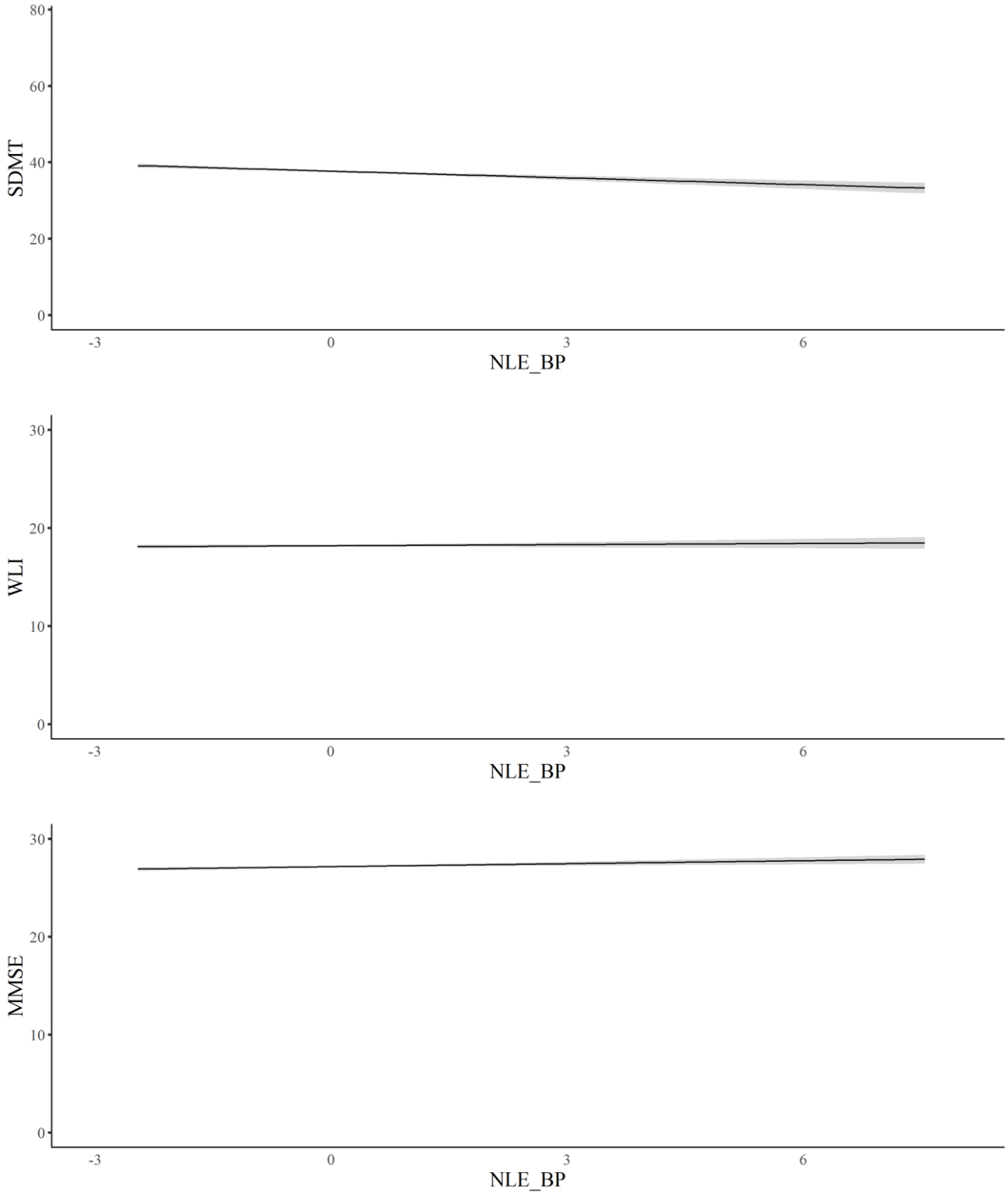


*Figure 5*. Between Person Effects of NLE on SDMT, WLI, and the MMSE in MAP

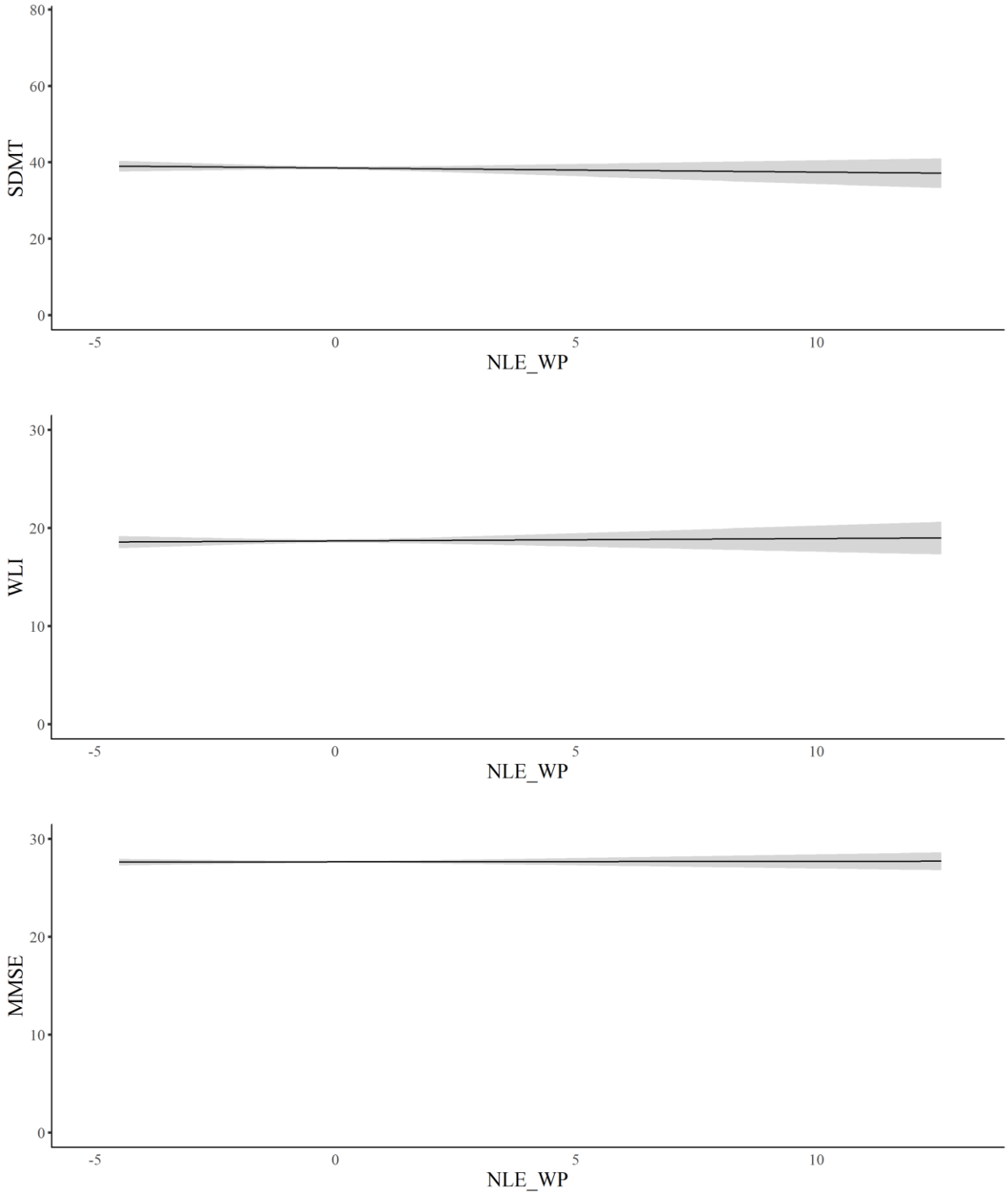


*Figure 6*. Within Person Effects of NLE on SDMT, WLI, and the MMSE in MAP

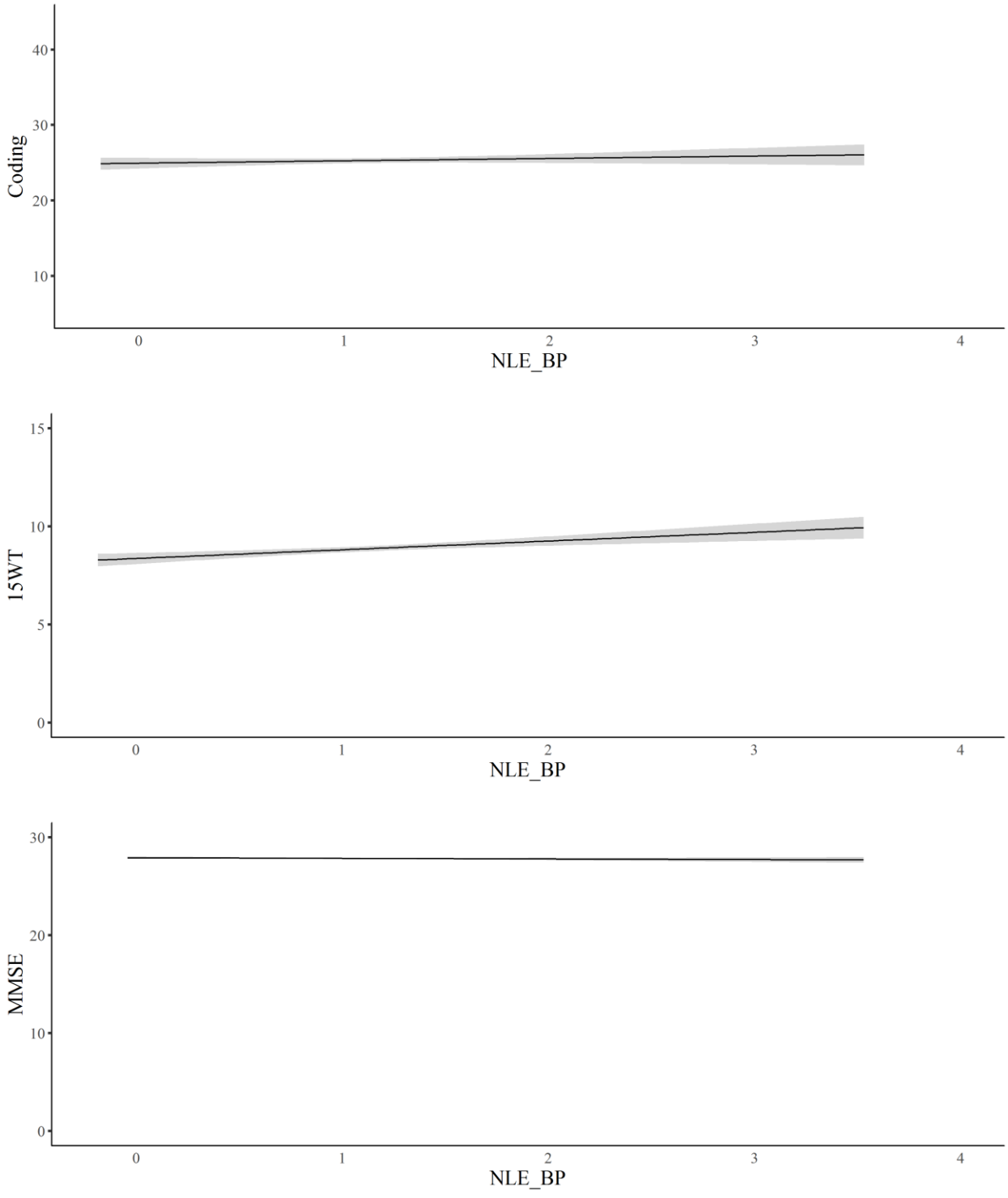


*Figure 7*. Between Person Effects of NLE on Coding, 15WT, and MMSE in LASA

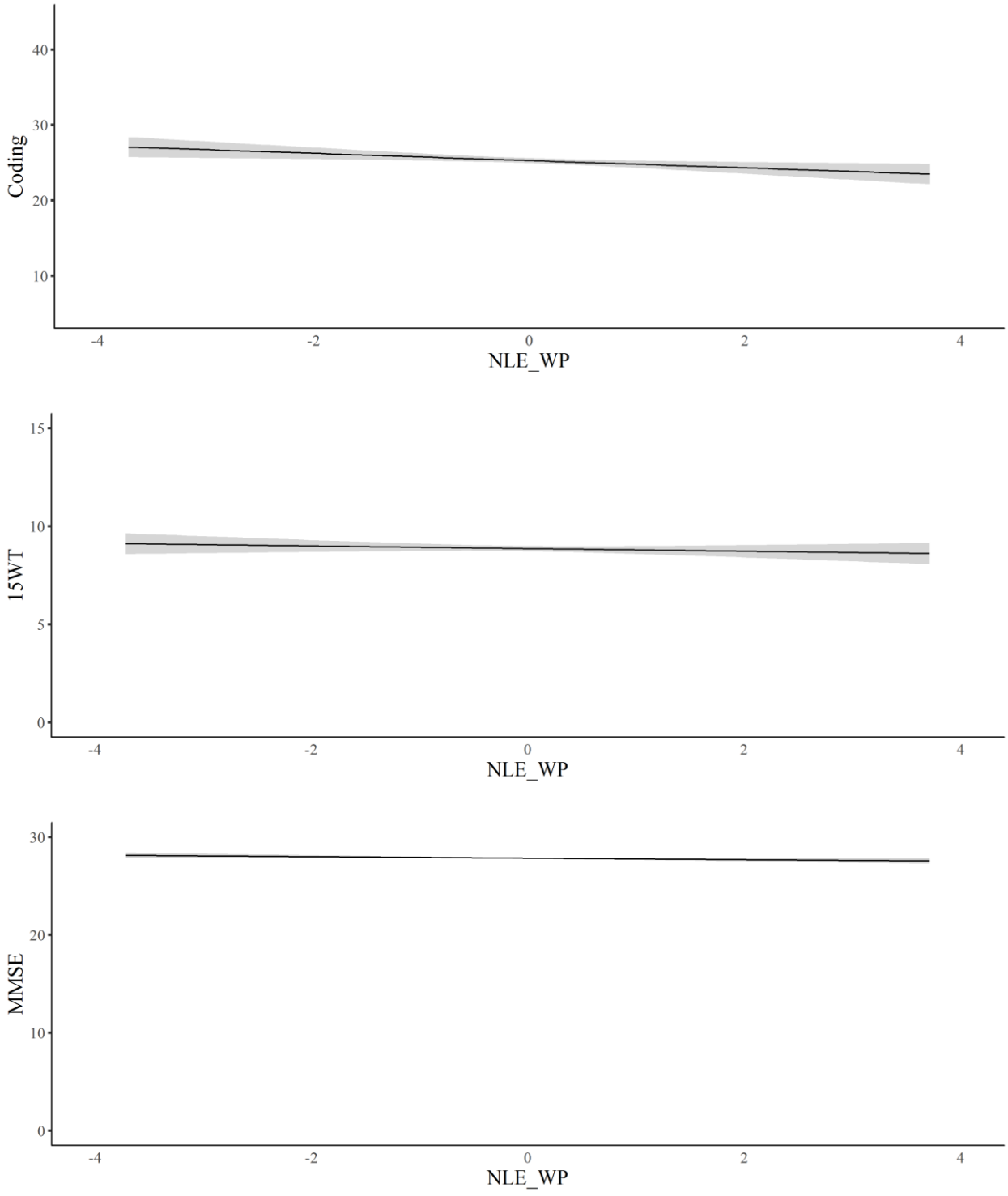


*Figure 8*. Within Person Effects of NLE on Coding, 15WT, and MMSE in LASA