THESIS

OCCUPATIONAL EXPERIENCES AND BRAIN HEALTH OUTCOMES IN OLDER AGE

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ABSTRACT

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Most adults spend half of their awake time at work. Although greater midlife work complexity has been consistently linked to better cognitive outcomes in older age, little is known about how occupational experiences associate with brain aging. Two studies have found an association between midlife managerial experience and slower hippocampal atrophy in older adults with no (Suo et al., 2012) and mild cognitive impairment (Suo et al., 2016) However, no study has considered to include both protective (enriching) and risk (stress-related) occupational factors in relation to neurocognitive health in aging, which we recently conceptualized as the BOSS model (Brain aging: Occupational Stimulation and Stress; Burzynska, Jiao, & Ganster, 2018). To empirically test this model, we assessed five stimulating and stress occupational constructs to reflect the characteristics of most recent main occupation in 101 cognitively healthy older adults (mean age=70, a subsample of "Fit & Active Seniors Trial (FAST)" trial, clinical study identifier NCT01472744). To obtain the above constructs, we did a priori grouping then factor analysis on 86 items from three well-established occupational experience questionnaires (Morgeson & Humphrey, 2006; Spector & Jex, 1998). We measured hippocampal volume with Magnetic Resonance Imaging and cognitive tasks with Virginia Cognitive Battery and spatial working memory tasks. Greater physical demand at work was associated with smaller bilateral hippocampi and lower performance on spatial working memory tasks, independent of the effects of age, education, estimated total intracranial volume, sensor-measured lifestyle moderate-to-vigorous physical activity, and current employment status. We found no evidence for greater

hippocampal volume or better cognition as a function of more stimulating occupational exposures. These findings have furthered our understanding of the neurocognitive correlates of physical demand in healthy older adults and also have highlighted the importance of using longitudinal measures in future studies to decipher the underlying neural mechanisms of occupational exposures.

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INTRODUCTION

Individuals who experience greater occupational complexity have been shown to have better age-related cognitive outcomes (Andel, Finkel, & Pedersen, 2016; Andel, Kåreholt, Parker, Thorslund, & Gatz, 2007; Bosma et al., 2003; Dartigues, Gagnon, Letenneur, et al., 1992; Dartigues, Gagnon, Mazaux, et al., 1992; Finkel, Andel, Gatz, & Pedersen, 2009; Oltmanns et al., 2017; Pool et al., 2016; Potter et al., 2015; Smart, Gow, & Deary, 2014; Then et al., 2015). Occupational complexity is often defined as work-related intellectual challenges and engagement based on the type of work duties, the degree of autonomy, and the scope of responsibilities of the individual (Finkel et al., 2009). This is a critical relationship, because age-related cognitive decline can lead to a significant decrease in life quality and independence (Vincent & Velkoff, 2010), thus posing a huge burden on the public health system and families. With a rapidly aging population, such public health challenges will likely be exacerbated as the United States is projected to have 78 million Americans aged 65 and older by 2035, about 30 million more than in 2015 (the US Census Bureau, 2017). Given the large proportion of an adult's waking hours spent at work (e.g., an average full time American worker spent 8.56 hours at work per weekday; Bureau of Labor Statistics, 2017), one's occupational experiences is thus poised to be an important factor in understanding neurocognitive aging (Staudinger, Finkelstein, Calvo, & Sivaramakrishnan, 2016). However, although some research suggests that stimulating occupational experiences are positively associated with age-related brain health (Suo et al., 2016; Suo et al., 2012), much remains to be understood. Therefore, the goal of this study is to identify occupational protective and risk factors for brain health and cognitive functioning in older age. To accomplish this, we used a theoretical framework that incorporates both positive and negative

occupational influences on brain and cognitive health, called the BOSS model (Brain Aging: Occupational Stimulation and Stress; modified model in Figure 1).

Following the BOSS model, we examined the role of occupational stimulation (perceived control, complexity, work significance, achievement, personal development, and constructive critique) and stress (workload, interpersonal conflict, environmental hazards, and physical demand) in associations to structural brain health and cognitive abilities. Occupational experiences were assessed using retrospective work history questionnaires and compared with the baseline hippocampal volume and cognitive ability in the Fit & Active Seniors Trial (FAST) sample of cognitively healthy older adults. We focused on the hippocampal volume because of its well documented vulnerability to aging (Fjell et al., 2009; Raz et al., 2005; Scahill et al., 2003). Understanding the role of occupational factors that accelerate or postpone neurocognitive aging is critical for developing successful workplace programs and interventions to support successful cognitive aging.

LITERATURE REVIEW

One's occupational experiences over the course of a long working life, comprise a variety of cognitive, social, and physical demand. While some of these demands are hypothesized to stimulate the brain and produce added resilience as one ages, others may pose physiological burdens that diminish one's ability to maintain a high level of cognitive functioning.

On a positive note, studies that have examined occupational complexity showed its positive association with cognitive functions. For example, Dartigues et al. (1992a, b) and Bosma et al. (2003) have focused on intellectually-demanding job experiences by using job title as a proxy for direct measurements of job experiences. They found that more intellectually demanding occupations (e.g., professional/managerial) are associated with higher cognitive functioning and lower cognitive decline than less intellectually-demanding occupations (e.g., farmers, domestic service, and blue-collar workers). Similarly, Bauer & Hämmig (2014) observed that episodic memory was better in middle-aged and older workers who had more control over the tasks they performed. Additionally, Andel et al, (2007), Jonaitis et al, (2013), and Smart et al, (2014) investigated occupational complexity at the occupational level using coded characteristics (data, people and things) from the Department of Labor database; they found that higher occupational complexity was associated with better cognitive performance, specifically, on memory performance and processing speed in later life. More recently, Oltmanns et al. (2017) showed that high rates of change in work tasks over time (novelty) were associated with better cognitive performance in processing speed and working memory in middle-aged and old-aged production workers. In summary, across different operationalizations of occupational complexity, and for a variety of cognitive functioning measures, evidence suggests that

occupational complexity is positively associated with cognitive performance in older workers. Furthermore, the positive association between occupational complexity and cognitive outcomes implies the importance of identifying the underlying neural mechanisms involved in this relationship.

Some research has also explored the underlying brain physiology that may associated with the effects of occupational experiences on cognitive functioning. Assessing the structural characteristics of the brain using magnetic resonance imaging (MRI) is one way to non-invasively measure brain health in aging adults. For example, Suo et al. (2012) used whole-brain (MRI voxel-based morphometry analysis) and found that occupying high-responsibility positions (high supervisory experience supervised more than 10 people) in mid-life might have a protective effect on the aging brain. More specifically, they demonstrated that working in a supervisory position in midlife, as assessed by the Lifetime of Experiences Questionnaire (LEQ; Valenzuela & Sachdev, 2007), was correlated with greater hippocampal volume in non-demented healthy adults aged 70 years or older. In addition, 91 of the 151 participants were followed for 2–3 years and the rate of hippocampal atrophy was five-times slower in those with high-level supervisory experience compared to those with no midlife supervisory experience. Despite supportive evidence that occupational experiences characterized by a specific level of complexity might forestall the effects of brain aging, non-supportive evidence has also been reported. For example, Foubert-Samier et al. (2012) measured cerebral and white matter volume in 331 non-demented participants aged 65 years or older. Among education, occupation, and leisure activities, only education (but not occupation) was positively associated with cerebral volume (white and gray matter). This apparent inconsistency may be due to the fact that different assessments of occupation were used in these two studies. In the Foubert-Samier et al. (2012)

study, occupation data were collected based on a 10-level International Standard Classification of Occupations (ISCO-88) (International Labour Organization, 1988), coded into "intellectual," "mixed," "elementary," and "housewife," and then grouped into two, "high" and "low" status. In addition, they did not specify the occupational period that was assessed (e.g., mid-life, main-life, or recent). Thus, a relatively coarse measure of occupational experience and a lack of information about supervisory tasks or other work characteristics may have diluted the occupational effects in this study. Moreover, this study might also highlight the importance of controlling for factors that typically covary with occupational complexity—such as education level—and those factors might be potent predictors of brain health in older adults. In general, the limited evidence suggests that being employed in an occupation that entails cognitive stimulation and challenges provide a measure of preserving brain health, which explains the positive development of the aging side of the BOSS model. Considerable evidence and further testing of the model are needed in validating such an assumption.

An approach that has been less often studied is to focus on the occupational experiences that reflect stressful work characteristics, such as overly high workloads, interpersonal conflicts, or physical demand. Such stressful occupational exposures reflect the factors that promote the negative development of aging side of the BOSS model, and there is a paucity of research that attempts to link midlife stress to brain health and cognitive functioning at later stages of life. Similar to research on the stimulating characteristics of occupation, it is important to determine the independent associations of the different stressful characteristics of occupation with neurocognitive outcomes in older adults. Cross-sectional studies have shown that middle-aged individuals who experience work-related chronic stress or burnout had lower memory, attention, and learning abilities than their non-stressed peers (Sandström, Rhodin, Lundberg, Olsson, &

Nyberg, 2005; Scott et al., 2015). Similarly, compared to those who had an intellectually-demanding job, such as managers and professionals (Dartigues et al., 1992 a,b), studies have demonstrated that people working in jobs that require significant physical effort and that primarily consist of routine tasks (Foubert-Samier et al., 2012), as well as those working in physically-demanding jobs, such as blue collar and domestic workers, had lower cognitive performance and higher risk for cognitive impairment (French version of the mini-mental state examination <24, Bier et al., 2005). Moreover, there is even some longitudinal evidence that job factors, such as a low level of job control, are associated with reduced cognitive performance and a higher decline in cognitive abilities, particularly around retirement age (Andel et al., 2015). The existing evidence on occupational stress and brain health are limited to occupational chronic stresses and concurrent brain health, and these associations have not been extended to an old age. For example, chronically-stressed middle-aged workers show reductions in the grey matter volumes of the anterior cingulate cortex and the dorsolateral prefrontal cortex (Blix et al., 2013) and reduction in caudate volume, the thinning of the medial prefrontal cortex (Savic, 2015). Furthermore, as the intensity and duration of stress increases (e.g., mild to chronic stress), the negative effects may be exacerbated by an association with brain shrinkage, such as that of the hippocampus, which can, subsequently, impair hippocampal-dependent memory task (Kim, Pellman, & Kim, 2015). Additionally, animal studies have shown that prolonged exposure to stress and elevated levels of glucocorticoids may reduce hippocampal neurogenesis, decrease the hippocampal neuronal survival rate, and damage dendritic arborization (Castilla-Ortega et al., 2011; Lupien, McEwen, Gunnar, & Heim, 2009). Thus, studies have shown evidence that occupational chronic stress or burnout is associated with negative changes in brain structure in

middle-aged adults, but additional research is needed to extend this investigation to whether the main life occupation could have an association with brain health in old age.

Both brain atrophy and cognitive decline are shown to occur both in normal and secondary (pathological) aging conditions. Without developing any diagnosed dementia or any brain pathology, individuals manifest cognitive decline that varies based on their cognitive reserve. According to the cognitive reserve hypothesis of cognitive aging (Hertzog, Kramer, Wilson, & Lindenberger, 2009; Stern, 2002, 2009), preexisting reserves may be built from high education level, premorbid IQ, stimulating occupational experiences, and a cognitively-engaged lifestyle, to formulate the interpretation of individual levels of cognitive, functional, or clinical differences associate with aging and brain pathology. Thus, it is difficult to determine whether a person's occupational-stimulating experience is an isolated factor that contributes to cognitive functioning, or whether it is closely associated with other socioeconomic and lifestyle factors. For example, people with higher education tend to have more cognitively stimulating occupations (White, St. John, Cheverie, Iraniparast, & Tyas, 2015).

Furthermore, it has been established that aerobic physical activity (PA) is positively linked to brain function (Voss et al., 2013) and cognitive health (Young, Angevaren, Rusted, & Tabet, 2015). For this study, in order to tease apart aerobic activity's competing role with other protective neurocognitive factors (e.g., education), we looked at one type of aerobic PA expressed in MVPA, because: 1) studies looked at MVPA shown direct benefits to brain health and memory functions (Daly, McMinn, & Allan, 2014; Klaren et al., 2015); 2) the general PA recommendation is that adults should engage in 30min/day on 5 days/week of moderate activity or 20 min/day on 3 days/week of vigorous activity, or a combination of moderate and vigorous activity to reach a similar amount (Haskell et al., 2007).

On the contrary, a lesser-studied factor is employment status around retirement age, namely, whether prolonged employment is beneficial for brain and cognition at older age. Few existing studies have found a positive association between prolonged employment beyond the typical retirement age and general cognitive function (Bonsang, Adam, & Perelman, 2012; Rohwedder & Willis, 2010). Moreover, some studies showed that only certain types of cognitive function are associated with prolonged retirement age (Denier, Clouston, Richards, & Hofer, 2017), or only apply to older adults with a particular type of job before retirement (e.g., jobs high in complexity with people; Meng, Nexø, & Borg, 2017). Therefore, when studying the occupational experiences and their associations with the brain and cognitive health in older adults, it is important to include covariates such as education, lifestyle aerobic physical activity, and employment status.

In this study, we decided to focus the study of occupational experiences on the hippocampus, because hippocampal shrinkage is considered a hallmark of normal aging (Fjell et al., 2009; Raz et al., 2005; Scahill et al., 2003), which is associated with cognitive impairment in late adulthood (Leung et al., 2010). In particular, the hippocampus has a well-documented role in human memory functions (O'Shea, Cohen, Porges, Nissim, & Woods, 2016; Raz et al., 2005) and various cognitive functions (Rubin, Watson, Duff, & Cohen, 2014; Eichenbaum & Cohen, 2001). In studies on the human brain, the hippocampus is believed to maintain neurogenesis in older adults, albeit at a reduced rate than is found in young adults (Boldrini et al., 2018; Riddle & Lichtenwalner, 2007). Animal studies have reported that an enriched environment (e.g., an environment that engages the brain by constant stimulations) increases the neurogenesis of granule cells in the dentate gyrus of adult mice, which are likely to be associated with improved hippocampus-related cognitive functioning (Brown et al., 2003; Garthe, Roeder, &

Kempermann, 2016). In contrast, exposure to stress at work may have negative impacts on cognitive functioning and the hippocampus (Kim et al., 2015). These types of stress exposures are especially important when they are chronic, as during the course of a long career. Chronic stress can lead to an elevated level of glucocorticoids, which bind to its receptors in the hippocampus, and leading to reduced size (Kim et al., 2015). This reduced hippocampal volume, particularly in the anterior part (Rajah, Kromas, Han, & Pruessner, 2010), has been related to poorer retrieval of the spatial and temporal contexts of episodic memory with increasing age. Thus, the hippocampus may be an ideal target brain structure to study the potentially overlapping yet contradictory relationships between long-term occupational stimulation and stress on brain health in later life.

Aims and Hypotheses

In the present, our study aimed at testing the association of both stimulating and stressful occupational exposures with cognition and hippocampal health. Following the BOSS model, we hypothesized that there is 1) a positive association between occupational stimulating factors and hippocampal volume and cognitive functions; 2) a negative association between occupational stress and hippocampal size and cognitive functions in late life.

METHODS

Participants

The participants for this study were part of a randomized controlled exercise trial, FAST (ClinicalTrials.gov, clinical study identifier NCT01472744). The study was approved by the University of Illinois institutional review board, verbal informed consent was obtained from all participants, and the study was performed in accordance with the 1964 Declaration of Helsinki. Participants were recruited from Champaign County in Illinois to participate in a 6-month program. A series of neuroimaging, cognitive, lifestyle and cardiorespiratory testing was conducted before and after the 6-month intervention program. Eligible participants met the following inclusion criteria for the intervention study and MRI assessment: (1) were between the ages of 60 and 79 years old; (2) were free from psychiatric and neurological illness and had no history of stroke or transient ischemic attack; (3) scored greater than 21 on the Telephone Interview of Cognitive Status (TICS-M) questionnaire (Fong et al., 2009), and greater than 23 on the Mini-Mental State Examination (MMSE, Lezak, Howieson, & Loring, 2004); (4) scored less than 10 on the geriatric depression scale (GDS-15, Sheikh & Yesavage, 1986); (5) scored at least 75% right-handedness on the Edinburgh Handedness Questionnaire (Oldfield, 1971); (6) demonstrated normal or corrected-to-normal vision of at least 20/40 and no color blindness; (7) were suitable for the MRI environment; that is, no metallic implants that could interfere with the magnetic field or cause injury, no claustrophobia, and no history of head trauma; (8) reported low or no physical activity (maximum of two moderate bouts of exercise per week) within the past six months. Of the 1,119 participants recruited, 872 participants were excluded based on the criteria described above. The remaining 247 participants were randomized into the four

intervention groups. Among the 247 participants who underwent MRI at the baseline, 234 yielded good quality structural MRI data, 234 finished Virginia Cognitive Aging Project Battery, 201 had valid spatial working memory data, and 229 had valid accelerometer data. The data were collected in 2011-2014.

To collect data on occupational experiences, in early 2017 we re-contacted the participants who had valid baseline structural MRI data and indicated their interest in follow-up assessments. 101 participants (Table 1) returned the completed work history questionnaire. In addition, all 101 participants met the additional criterion of MMSE >26 to exclude adults with possible mild cognitive impairment (Marioni, Chatfield, Brayne, Matthews, & Medical Research Council Cognitive Function and Ageing Study Group, 2011).

Measures

Work-related History Questionnaire

In order to have a broad and systematic measurements of the occupational experiences of individual's most recent main occupation, we selected eighty-six items from three scales: (1) Interpersonal conflict scale, a four-item scale developed by Spector & Jex (1998); (2) Work load, a five-item scale developed by Spector & Jex (1998) and (3) Work Design Questionnaire (WDQ), a seventy-seven-item questionnaire developed by Morgeson & Humphrey (2006). These questionnaires were selected because the included measures of work characteristics have been well-established and validated, and widely used by researchers (Bayona, Caballer, & Peiró, 2015; Wright et al., 2017). Participants were instructed to answer these questions concerning the most recent main job that they had been performing (full time or part-time) for more than two years, due to the fact that participants may have more accurate memory about the most recent main job (Park & Festini, 2017). The eighty-six items were identified from three questionnaires as reflecting stimulating and stressful characteristics, then subsequently divided into 10 sub-

categories. Stimulating work characteristics included complexity, personal development, significance, perceived control, achievement, and constructive critique. Stressful work characteristic included workload, environmental hazards, interpersonal conflict, and physical demand. Individual questions, measurement scales, and sources of each group of questions are listed in Table 2.

To make sure that the assessed questions in each sub-category produce stable and consistent results, we tested internal consistency. Cronbach's alpha (α) test was selected, it is a measure of construct consistency, that is, how closely related a set of questions are as a sub-category. Cronbach's α was high for all ten sub-categories (perceived control, α = .96; complexity, α =.93; work significance, α = .85; achievement, α = .91; personal development, α = .84; constructive critique α = .92; workload, α = .86; interpersonal conflict, α = .77; environmental hazards, α = .82; and physical demand, α = .94).

Occupational Experience Sub-categories: Confirmatory Factor Analysis

Table 3 showed the ten sub-categories of occupational experiences as described above. We observed moderate intercorrelations among them, indicating certain conceptual and statistical overlap, which may be driven by a smaller number of latent variables, i.e. the variables were not directly measured but inferred from other measured variables. Therefore, to confirm the *a priori* latent structure of occupational variables, we performed a principal component analysis (PCA) on the ten occupational sub-categories with a varimax rotation. All ten sub-categories had high loadings on the three-factor components (Table 3). The first factor, which we named "cognitive stimulation" was defined by high loadings on planning, control, complexity, significance, achievement, personal development, and constructive critique. The second factor, named "physical and environmental stress" was defined by high loadings on environmental

hazards and physical demand. The last factor, "psychological stress" was defined by high loadings on workload and interpersonal conflict. Internal reliability was high for the "cognitive stimulation" (α =.79), but lower for "psychological stress" (α = .51) and "physical and environmental stress" (α = .34). In sum, the factor analysis conformed the latent structure of our dataset. In order to retain maximum reliability of the occupational factors in the analyses, we used the original *a priori* four occupational stress sub-categories: cognitive stimulation (α =.79) and the four stress factors: workload (α = .86), interpersonal conflicts (α = .77), environmental hazards (α = .82), and physical demand (α = .94).

Employment Status (ES)

Among 101 participants who returned the questionnaires, 50 participants indicated their employment status as employed, which means they were either full time employed, retired and full time employed, or retired but part time employed (coded as 1). The remaining 51 participants indicated that they were fully retired (coded as 2), which means they did not engage in any paid work at the time of the study.

MRI Acquisition

Images were acquired during a single session on a 3 T Siemens Trio Tim system with 45 mT/m gradients (Siemens, Erlangen, Germany). Structural MRI scans were acquired using a 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) T1-weighted sequence: repetition time (TR) = 1900 ms; echo time (TE) = 2.32 ms; inversion time (TI): 900 ms; flip angle = 9°; matrix = 256 × 256; field of view (FOV) = 230 mm; 192 slices; resolution = 0.9 × 0.9 × 0.9 mm; GRAPPA acceleration factor 2.

MRI Data Processing

Automated brain tissue segmentation and reconstruction of cortical models was performed on T1-weighted images using the Freesurfer software, version 5.3 (http://surfer.nmr.mgh.harvard.edu/). In brief, individual T1-weighted images underwent non-brain tissue removal, Talairach transformation, creation of representations of the gray/white matter boundaries (Dale & Sereno, 1993; Bruce Fischl, Sereno, & Dale, 1999) and calculation of the cortical thickness as the distance between the gray/white matter boundary at each point across the cortical mantle(B Fischl & Dale, 2000). AZ Burzynska screened all surface reconstructions to evaluate the success and plausibility of the automatically processed results, as recommended by the software developers. Finally, volumes of eTIV and hippocampus were extracted per individual. eTIV was used as a covariate to control for gender and individual differences in brain size. Total volume of hippocampus was calculated as the sum of bilateral hippocampal volumes.

Cognitive Testing: Virginia Cognitive Aging Project Battery

A battery from the Virginia Cognitive Aging Project (VCAP) was chosen to test cognitive performance. It involves tests of a variety of cognitive domains and consists of 16 tasks (Supplementary Table 1), they were either computer-based or pen and paper-based. The computer-based tasks were programmed in E-Prime version 1.1 (Psychology Software Tools, Pittsburgh, PA) and administered on computers with 17" cathode ray tube monitors. First, all 16 tasks for each participant were screened for outliers and winsorized (e.g. extreme values that are outside of the confidence intervals replaced by confidence intervals at 5% and 95%). Next, to confirm the validity of task structure described in Salthouse & Ferrer-Caja (2003), a PCA with varimax rotation was performed, four component scores were retained as final variables:

vocabulary, fluid intelligence, perceptual speed, and episodic memory (for more details on each task and PCA loadings see Supplementary Table 1), and consistent with the task structure described in Salthouse, 2004.

Spatial Working Memory

The spatial memory paradigm was used due to the fact that the hippocampus plays an essential role in spatial memory, which involves information recording and spatial orientation (MacDonald, Lepage, Eden, & Eichenbaum, 2011; Monti et al., 2015). At the start of the task, participants were shown a fixation crosshair for 1 second, followed by the appearance of 2, 3, or 4 dots placed in random locations on the screen. Two and 3-dot trials were displayed for 500 milliseconds, and sets of 4 dots were displayed for 1 second. Then, a 3 second fixation crosshair appeared, followed by the appearance of a red dot, which displayed for 2 seconds. Participants had to indicate whether the red dot displayed was in the same location (match) or a different location (non-match) than one of the previously presented black dots, by pressing a designated key on a computer keyboard. Participants completed a total of 120 trials, 40 trials per set size (2, 3, and 4 black dots), each containing 20 match and 20 non-match trials. Participants completed 12 practice trials (6 match, 6 non-match) prior to task administration to familiarize them with the task. Accuracy rates and response times were both recorded separately for the 2, 3, and 4 dot conditions and were averaged to created mean accuracy and response time scores.

Sensor-based PA

Sensor-based PA was collected by accelerometer (Model GT1M or GT3X; Actigraph, Pensacola, FL). Each participant was instructed to wear the accelerometer on the non-dominant hip during all waking hours for 7 consecutive days, and record the time that they wore the device each day on a log to ensure the quality measurements. These data were then downloaded as

activity counts, which represent raw accelerations that have been summed over a specific epoch length (60 s). Next, these data were processed using cut points designed specifically for older adults (Copeland & Esliger, 2009) such that 1,041 counts or greater represented MVPA.

STATISTICAL ANALYSES

General guidelines were followed by YJ and two research assistants in performing data cleaning. 1) Two research assistants from the BRAiN lab independently conducted accuracy checks of the manually entered data. 2) Visual checks were done for missing data; any detected missing data was coded as -999.99 on SPSS to label it as missing data. 3) SPSS was used to construct histograms for checking normality distributions (outliers that were outside of the confidence intervals replaced by confidence intervals at 5% and 95%).

Statistical analyses were performed using SPSS (v.25, SPSS Inc. IBM). To model the relationships between occupational exposures (independent variables), hippocampal volume and cognition (the dependent variables), we conducted a series of hierarchical linear regressions. In step 1, we entered age, gender (in the model with cognitive dependent variables), education, MVPA, ES, and eTIV (only for the model with hippocampal volume). In step 2, we entered occupational factors. In addition, in step 3, we entered quadratic terms of the occupational factors in order to accommodate potential non-linear associations. Bonferonni correction was used for multiple comparisons for correlations between the variables of interest

RESULTS

Comparison Between the Responders and Non-Responders

First, we tested the extent to which the responders in the current study (n=101) were representative of the full study sample (n = 247). Independent sample t-tests showed no group differences on age, gender composition, education, eTIV, cognition, and MMSE (all t tests had p values greater than 0.320).

Bivariate Correlations among Study Variables

We first carried out the analyses to test whether the lifestyle factors that are known to contribute to the CR associate with hippocampal volume and cognition. We did not find any significant association between the variables of interest and hippocampal volume, when controlling for age and eTIV. Similarly, we did not observe MVPA and employment status correlates of cognitive functions after controlling for age and education. Next, we examined the association between the five occupational factors and total hippocampal volume ($\alpha_{altered}$ = .05/5 = .01). After controlling for eTIV and age, only physical demand factor was marginally correlated to total hippocampal volume (r=-.256, p=.012, df=94). Similarly, only physical demand factor was correlated to spatial working memory accuracy (r=-.206, p=.040, df=97), after controlling for education and age. However, it did not survive Bonferroni correction. Such associations imply the needs to continue and investigate the associations of different occupational experiences with neurocognitive outcomes.

Occupational Factors and Hippocampal Volume

We first examined the association between the five occupational factors and total hippocampal volume. The model in Table 4 was designed to test physical demand as the main

independent variable in predicting hippocampal volume. We found that physical demand explained significant additional variance in total hippocampal volume (adjusted R^2= .304, ΔR^2=.048, F(10, 93) = 4.03, p=.019) after controlling for age, eTIV, education, MVPA, employment status, as well as the remaining four occupational factors.

Next, we tested whether the observed association was equally representative for left and right hippocampus by using the same model described above. Indeed, physical demand explained significant additional variance in left (adjusted R^2= .322, ΔR^2=.037, F(10, 93) = 3.948, p=.037) and right hippocampal volume (adjusted R^2= .210, ΔR^2=.024, F(10, 93) = 2.948, p=.018), after controlling for the same factors as described above (supplementary Table 2 and 3).

Occupational Factors and Cognitive Performance

Next, we examined the association between the five occupational factors and cognitive functions. Thus, we identified physical job demand as the only occupational correlate of memory function. We further examined the role of additional covariates in this association: education, MVPA, employment status, as well as the remaining four occupational factors. Result showed that physical demand explained significant additional variance in spatial working memory accuracy (adjusted R^2=.188, ΔR^2=.058, F(10, 96)=1.658, p=.016), after controlling for the above factors. However, this was not the case for episodic memory.

DISCUSSION

We examined the associations between recent occupational experiences and hippocampal volume and cognition in cognitively healthy older adults. We found evidence supporting the stress part of the BOSS model: physical demand at work were associated with smaller hippocampal volume and lower spatial working memory accuracy. These associations were independent of the effects of age, eTIV, education, employment status, and MVPA, and the remaining occupational factors. However, our data did not support the hypothesis of a positive association between occupational complexity and hippocampal volume. Here we discuss our findings in relation to the BOSS model and relevant existing literature

The hypothesis stated that occupational stress factors and hippocampal volume and cognitive functions are negatively associated. While physical demand at work was observed to have negative association with hippocampal volume and lower cognitive function, supporting previous studies that have examined the relationship between stress at work and neurocognitive health (Blix et al., 2013; Diestel, Cosmar, & Schmidt, 2013; Savic, 2015), in this study, physical demand was the only occupational stressor that showed such significant result. More specifically, physical demand was measured in a systematic way and described physical activities in occupational tasks that required more than the usual amount and/or duration of physical exertion, endurance, and strength (WQD, Morgeson & Humphrey, 2006). For example, question asks to rate the requirement of a great deal of muscular endurance at work. This measure filled the gap in the literature by emphasizing the importance of identifying stress resulting from diverse and complicated working conditions (e.g., workload and interpersonal conflicts) compared to those involved in physical labor (physical demand).

In particular, our finding suggests that most recent main life physical demand at work was negatively associated with hippocampal volume at an older age, which is consistent with previous human studies (Lupien et al., 2009; McEwen, 2001; Zimmerman et al., 2016). Blix et al., (2013) found a significant association between chronic psychosocial stress at work and volume reductions in the regions of gray matter among mid-aged adults. Similarity, among mid-aged workers, Savic (2015) suggested that chronic burnout at work is associated with cortical thinning. However, such findings focus on one type of assessment of occupational stress might not fully capture neurocognitive development at later age (Blix et al., 2013; Savic, 2015). In addition, research has shown that in a longitudinal setting, perceived stress at work was related to a smaller hippocampal volume (Lindgren, Bergdahl, & Nyberg, 2016), but participants who experienced high levels of perceived stress at work were also tested to be comorbidly depressed or other emotional distress, which could make it difficult to determine if the comorbidity condition or the stressful events at work were related to brain health.

Moreover, our findings that physical demand was associated with worse cognitive function support the evidence that stress in general is associated with declines in cognitive performance(Diestel et al., 2013; Linden, Keijsers, Eling, & Schaijk, 2005). Few studies have attempted to focus on the physical stress component of the occupation, and those that have, only used occupational title as a proxy of the stress of the educational experience, which was linked to decreased cognitive functioning later in life (Dartigues et al.,1992a, b). We used a more detailed questionnaire to gather information about occupational stress including the physically demanding occupational experiences at the individual level of analysis. In the present study, stress was associated with worse spatial working memory, which is consistent with the study that found that basal cortisol elevation from stress may cause damage to the hippocampus and further impair its

dependent cognitive functions such as memory (Lupien et al., 2009; MacDonald et al., 2011). In sum, these findings are consistent with the theoretical perspectives of the BOSS model, which emphasizes the role of occupational stress in lower brain volume and worse cognitive performance.

However, inconsistent with previous literature (Andel et al., 2016; Bosma et al., 2003; Finkel et al., 2009; Oltmanns et al., 2017; Pool et al., 2016; Potter et al., 2015; Smart et al., 2014; Then et al., 2015), in this study, occupational cognitive stimulation was not associated with hippocampal volume or cognitive performance. In our study, occupational cognitive stimulation was derived as one factor from the high loadings of control, complexity, significance, achievement, personal development, and constructive critique. We argue that even with high occupational cognitive stimulation, the associated stress should also be evaluated to determine the balance between the amount of stress and stimulation that an individual experience at work. However, there is a lack of evidence in the literature on combining stimulating exposures and other proxies of reserve. This is generally supportive of one occupational exposure hypothesis, which suggests that stimulating exposure at work leads to better brain and cognitive health in later life (Andel et al., 2016; Finkel et al., 2009; Oltmanns et al., 2017; Potter et al., 2015; Suo et al., 2012, 2016). However, some factors, such as lifestyle factors, have not been addressed. For example, intellectual jobs may provide individuals with more time to engage in leisure activities, which are strongly protective against brain and cognitive declines (Andel et al., 2016). In addition, a large hippocampus may arise from stimulating work environments in early life, even if the environment changes to low stimulation during middle age, prior to the MRI session of the original study. More studies are needed to distinguish the relationships between occupational experiences, lifestyle factors, and related hippocampal changes as individuals age. Moreover, a

single measure of stimulating occupational exposure, such as supervisor experience, needs to be measured to continue investigating its impact with other stressful experiences as a whole and separately.

It was intriguing that higher physical demand at work was related to worse neural outcomes, given that MVPA is known to be linked with better memory and greater hippocampal volume (MVPA). Studies that measure the exercise at work are mainly focused on the non-aerobic activities to reduce musculoskeletal pain, such as pain in the shoulder and neck areas (Eerd, et al., 2016; Coury, Moreira, & Dias, 2009) or aerobic activities during the commute to and from work (Audrey, Procter, & Copper, 2014; Bassett, Pucher, Buehler, Thompson, & Crouter, 2008). In addition, certain jobs involve more physical activities, such activity may not necessarily be healthy: studies show that occupations involving high physical activities relate to worse health outcomes and increased risk for all-cause mortality (Holtermann, Hansen, Burr, Søgaard, & Sjøgaard, 2012; Holtermann et al., 2011; Krause et al., 2007). Our study corroborated the latter observations and showed that physical demand at work was associated with worse brain outcome at an old age, highlighting that physical demand at work and other types of physical activities, including aerobic exercises, should be measured separately in understanding the impacts on brain and cognitive health.

Although our findings suggest that education correlate with cognitive performance in vocabulary and fluid intelligence, it shows no correlation with hippocampal volume. Partially contrast to those studies that have shown that higher educational attainment is associated with greater brain volume and reduced cognitive decline in later life (Arenaza-Urquijo et al., 2013; Foverskov et al., 2018; Liu, Rovine, & Molenaar, 2012). However, some studies have cast doubt on the positive relationships OF (Lyketsos, Chen, & Anthony, 1999; Zahodne, Stern, & Manly,

2015). Specifically, it has been suggested that education that occurs after the most critical period of brain development in early age may not substantially impact later brain and cognitive health; rather, it appears that educational experience could provide an enriched environment for educational engagement to continue growth in cognitive abilities and maintain the brain's integrity throughout one's lifetime (Kremen et al., 2018). Therefore, occupational experiences may have a greater association with later-life neurocognitive health than educational attainment.

Lastly, we observed that employment status was not associated with hippocampal volume or cognitive functions in older adults. The findings are different from previous research that showed continued employment was positively associated with cognitive functions in older adults (Bonsang et al., 2012; Celidoni, Dal Bianco, & Weber, 2017; Rohwedder & Willis, 2010). Although we did not observe positive associations with neurocognitive outcomes among people who continue to work after retirement when compared with those who were fully retired, the lack of significance might have resulted from unknown information about the participants' decisions to either continue being employed or fully retired; thus, it was not possible to fully understand the impact of prolonged employment around retirement age (e.g., bridge jobs). For instance, Fisher, Ryan, & Sonnega, (2015) argued that people are more likely to continue working after retirement if they were involved in jobs that were stimulating or if they had a white-collar job. In addition, retirement-aged individuals who continue to work are involved in many types of engaged employments, such as full-time, part-time, and bridge jobs. Another factor that may hasten retirement decision is the negative changes in health. For example, studies have documented that poor health is considered as a big indicator of fully retirement pre- or post-retirement (McGarry, 2004; Wallace, Haveman, & Wolfe, 2017). In order to maintain substantial power for analysis, we retained the employment statuses as employed and fully retired. Future

studies should explore the effects of employment status on using more information about the types of jobs individuals choose to do after retirement.

Upon correlation of the proxies of CR into the correlation model, we observed that physical demand explained an additional variation in its association with hippocampus and cognitive performance. This result confirms the importance of including work experiences in future studies to understand the impacts on lifelong developments in both brain and cognitive health. It would be intriguing to continue to study whether the positive experiences of an occupation contribute to the CR and how such contribution competes with other well-documented factors, such as cognitively enriching activities (Chan et al., 2018). Such activities maintain high levels of cognitive performance in old age, associated with the maintenance of high levels of cognitive functioning in old age (Andel et al., 2016; Chan et al., 2018). It is possible that individuals who experience high stress levels at work may not obtain sufficient activities outside work in order to maintain brain health.

LIMITATIONS AND FUTURE DIRECTIONS

Although the study was conducted with rigor, limitations exist. First, the study's cross-sectional design did not allow us to address the causal relationship between occupational exposures and neurocognitive outcomes. It is possible that individuals with smaller hippocampal volume and lower cognitive abilities self-select into a most recent main life occupation with higher physical demand or the significant findings obtained in this study could be the result of a convenience sample that included individuals with more physically demanding occupational experiences. As shown in our data, the distribution of physical demand scores is moderately positive skewed (skewness=.692).

Another limitation of this study is the retrospective self-reported work history questionnaire that was used. We acknowledge that the responses might not be an accurate representation of the older participants' last main occupational exposures. For example, the responses might have been impacted due to the decline in the participants' memory functions and the age-related positivity effect related to memory retrieval (Reed & Carstensen, 2012). Ideally, future studies should start at middle age and follow participants in a longitudinal fashion, thus avoiding the pitfalls of retrospective data collection.

Third, the questionnaire did not directly assess the participants' supervisory experience in terms of the number of supervised workers, which has been shown to have a positive association with greater hippocampal volume and reduced hippocampal shrinkage (Suo et al., 2012). Future studies should examine the differences in the supervisory experiences of the participants in relation to their neurocognitive outcomes in order to continue testing the stimulating part of the BOSS model.

Fourth, the current study did not measure leisure activities outside of work (e.g., use validated questionnaire Lifetime of Experience Questionnaire; Valenzuela & Sachdev, 2007) along with the occupational experiences of their most recent main life occupation, which is an important aspect of cognitive reserve (Andel et al., 2015, Stern, 2009). This limited our ability to understand influences external to work and whether such influences compensate or compete with occupational experiences. Therefore, it would be valuable to extend the associations that were observed here and link them to the leisure activities an individual was involved in order to identify the ways in which they interacted with each other.

Next, the participants were asked to indicate the most recent main occupation that they have been primarily performing for more than 2 years. This might not be representative of their main life occupation or best express their longest occupational experiences. Ideally, in future studies occupational experience would be assessed throughout the participants' lifespan to ensure that data on the most instrumental occupation and its related occupational exposures are obtained. Some studies show that midlife educational experiences are crucial factors in linking to cognitive health(Stern, 2012; Wang, MacDonald, Dekhtyar, & Fratiglioni, 2017). In our sample, the length of occupation ranged from 1 to 51.5 years, with close to half of the individuals sharing occupational experiences in jobs that they might start in middle age. However, due to a lack of consistency in clearly identifying whether the most recent occupation was interpreted as the midlife occupation, we identified the occupational experience as the most recent main occupation. It would be invaluable to further distinguish the two terminologies in future studies in occupational neuroscience.

Lastly, we included MVPA to control for the aerobic physical exercise. The aerobic exercise may not be the best representation of the physical activities involved at a workplace and

unable to distinguish the aerobic exercises at work and outside work from the current analysis plan. Ideally, physical data should be collected on weekdays and weekends to account for variation in physical activity at work and during time off. In the future, data about the different types of aerobic and non-aerobic exercises should be collected separately, or participants must be instructed to record the times their devices are worn during or outside work to have a better understanding of whether different types of exercises exert competing effects in between the occupational experiences and neurocognitive outcomes. In addition, other types of physical activity should be considered alongside existing activity. For example, light physical activity may be observed more at work than in other environments. Because such activities are the ones most likely for individuals to engage at work (Buman et al., 2017).

Ideally, in the future, researchers should implement prospective longitudinal designs that can follow individuals from young adulthood to later life while assessing the roles of occupational experiences, brain health, and cognitive performance, and collecting lifestyle factors that people engage in outside of work for a full understanding of occupational experiences and neurocognitive outcomes. Although such studies are highly difficult to conduct, they can nevertheless provide crucial information for employees in all age groups and their employers about executing appropriate strategic procedures in securing a healthy and successful aging development, and mitigating the negative correlates of occupational stress by recommending information or resources that compensate or preserve individuals' brain and cognitive health.

CONCLUSION

To the best of our knowledge, this is the first study to consider both occupational stimulation and stress factors in neurocognitive outcomes in older age. We examined whether occupational experiences were associated with neurocognitive outcomes in older adults by following the theoretical framework of the BOSS model. The findings show the importance of identifying occupational factors that moderate the course of neurocognitive aging. This knowledge could facilitate development of workplace interventions for both the young and older workers, to optimize the aging experience.

Table 1

Participant demographics (n=101)

	N	Minimum	Maximum	Mean	Standard Deviation
Age	101	64	84	69.97	4.64
Female	101	71%			
Years of education	101	12	26	16.24	3.06
Total hipp [mm^3]	98	6484.00	10140.30	8305.37	845.55
eTIV [mm^3]	98	160905.41	2545657.64	1448013.04	219803.30
MVPA (min/day)	99	4.67	141.71	47.35	31.05
Cognition					
Fluid intelligence	101	-2.090	2.094	-9.615e -17	1.000
Vocabulary	101	-2.644	1.906	2.773e -16	1.000
Episodic memory	101	-2.185	2.505	-6.109e -16	1.000
Perceptual speed	101	-1.837	2.551	2.355e -16	1.000
SPWM reaction time	101	-2.595	2.538	6.673e -16	0.995
SPWM accuracy	101	-4.159	1.273	-7.628e -16	0.995

Note. Four cognitive constructs are PCA derivatives. SPWM: spatial working memory.

Table 2

Stimulating and stressful work exposures: questionnaire design

Occupational factors	Reference
1. Perceived Control (stimulating)	
The job allowed me to make my own decisions about how to schedule my work.	WDQ (Morgeson & Humphrey, 2006)
The job allowed me to decide on the order in which things were done on the job.	
The job allowed me to plan how I did my work.	
The job gave me a chance to use my personal initiative or judgement in carrying out the work.	
The job allowed me to make a lot of decisions on my own.	
The job provided me with significant independence in making decisions.	
The job allowed me to make decisions about what methods I used to complete my work.	
The job gave me considerable opportunity for independence and freedom in how I did the work.	
The job allowed me to decide on my own how to go about doing my work.	
2. Complexity (stimulating)	
The job involved a great deal of task variety.	WDQ
The job involved doing a number of different things.	
The job required the performance of a wide range of tasks.	
The job involved performing a variety of tasks.	
The job required that I only do one task or activity at a time (reverse).	
The tasks on the job were simple and uncomplicated tasks (reverse).	
The job comprised relatively uncomplicated tasks (reverse).	
The job involved performing relatively simple tasks (reverse).	
The job required a variety of skills.	
The job required me to utilize a variety of different skills in order to complete the work.	
The job required me to use a number of complex or high-level skills.	
The job required the use of a number of skills.	
The job is highly specialized in terms of purpose, tasks, or activities.	

The tools, procedures, materials, and so forth used on this job were highly specialized in terms of purpose.	
The job required very specialized knowledge and skills.	
The job required a depth of knowledge and expertise.	
The job involved the use of a variety of different equipment.	
The job involved the use of complex equipment or technology.	
A lot of time was required to learn the equipment used on the job.	
The job required me to monitor a great deal of information.	
The job required that I engaged in a large amount of thinking.	
The job required me to keep track of more than one thing at a time.	
The job required me to analyze a lot of information.	
The job involved solving problems that have no obvious correct answer.	
The job required me to be creative.	
The job often involved dealing with problems that I had not met before.	
The job required unique ideas or solutions to problems.	
3. Significance (stimulating)	
The results of my work were likely to significantly affect the lives of other people.	WDQ
The job itself was very significant and important in the broader scheme of things.	
The job had a large impact on people outside the organization.	
The work performed on the job had a significant impact on people outside the organization.	
4. Achievement (stimulating)	
The job required me to accomplish my job before others completed their job.	WDQ
Other jobs depended directly on my job.	
Unless my job got done, other jobs could not be completed.	
The job activities were greatly affected by the work of other people.	
The job depended on the work of many different people for its completion.	
My job could not be done unless others did their work.	
5. Personal development (stimulating)	

I had the opportunity to develop close friendships in my job.	WDQ
I had the chance in my job to get to know other people.	
I had the opportunity to meet with others in my work.	
My supervisor was concerned about the welfare of the people that worked for him/her.	
People I worked with took a personal interest in me.	
People I worked with were friendly.	
The job required spending a great deal of time with people outside my organization.	
The job involved interaction with people who were not members of my organization.	
On the job, I frequently communicated with people who did not work for the same organization as I did.	
The job involved a great deal of interaction with people outside my organization.	
6. Constructive critique (stimulating)	
I received a great deal of information from my manager and coworkers about my job performance.	WDQ
Other people in the organization, such as managers and coworkers, provided information about the effectiveness (e.g., quality and quantity) of my job performance.	
I received feedback on my performance from other people in my organization (such as my manager or coworkers).	
7. Workload (stress)	
How often did your job require you to work very fast?	Workload
How often did your job require you to work very hard?	scale
How often did your job leave you with little time to get things done?	(Spector &
How often was there a great deal to be done?	Jex, 1988)
How often did you have more work than you could do well?	
8. Interpersonal conflict (stress)	

How often did you get into arguments with others at work?	Interpersonal
How often did other people yell at you at work?	conflict scale
How often were people rude to you at work?	(Spector &
How often did other people do nasty things to you at work?	Jex, 1988)
9. Environmental hazards (stress)	
The seating arrangements on the job were adequate (e.g., ample opportunities to sit, comfortable chairs, good postural support) (reversed).	WDQ
The work place allowed for all size differences between people in terms of clearance, reach, eye height, leg room, etc (reversed).	
The climate at the work place was comfortable in terms of temperature and humidity (reversed).	
The job had a low risk of accident (reversed).	
The job took place in an environment free from health hazards (e.g., chemicals, fumes, etc.) (reversed).	
The job occurred in a clean environment (reversed).	
The work place was free from excessive noise (reversed).	
10. Physical demand (stress)	
The job involved excessive reaching.	WDQ
The job required a great deal of muscular strength.	
The job required a lot of physical effort.	
The job required a great deal of muscular endurance.	

Note. 5-point response scales were used for all questions (1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Quite often, 5 = Very often)

Table 3

Confirmatory factor analysis (PCA) on ten occupational sub-categories.

Measurements	Cognitive stimulation	Physical and environmental stress	Psychological stress
Workload			.718
Interpersonal conflicts			.842
Control	.668		
Complexity	.798		
Significance	.692		
Achievement	.672		
Personal development	.731		
Constructive critique	.664		
Environmental hazards		.811	
Physical demand		.809	
Proportion of variance	33.32	19.09	11.33
Cumulative proportion of variance	33.32	52.41	63.74

Note. For clarity, only loadings above 0.50 are displayed. Rotation: varimax.

Table 4

Occupational factors of total hippocampal volume

	Step 1	Step 2	Step 3	Step 4
	B	B	B	B
Age	-75.374***	-75.886***	-68.232**	-67.369**
Education	12.669	7.354	-1.453	-6.249
MVPA	1.617	3.329	4.154	1.637
Employment status	-53.040	-54.940	-69.072	-92.745
eTIV	.001	.001	.001	.001
Work stimulation		83.602	141.841	132.260
Workload		-113.599	-68.470	61.153
Interpersonal conflicts		209.902	201.397	1334.611
Environmental hazards		-23.075	1.275	-121.026
Physical demand			-218.459*	-696.648
Work stimulation (quadratic term)				49.511
Workload (quadratic term)				-18.511
Interpersonal conflicts (quadratic term)				-343.026
Environmental hazards (quadratic term)				86.975
Physical demand (quadratic term)				3.464
R_2	.223	.256	.304	.355
ΔR_2		.033	.048*	.051

*Note: * p < .05 (2-tailed). ** p < .01(2-tailed). *** p < .001*

Table 5

Occupational factors of spatial working memory *accuracy*

	Step 1	Step 2	Step 3	Step 4
	B	B	B	B
Age	.004	-.005	.001	-.001
Education	.036	.020	.006	.004
Gender	-.069	-.100	-.179	-.173
MVPA	.007	.009*	.009*	.008
Employment status	-.068	-.048	-.068	-.052
Work stimulation		.131	.198	.194
Workload		.030	.106	.374
Interpersonal conflicts		-.304	-.357	-1.958
Environmental hazards		-.018	.012	.060
Physical demand			-.272*	-.442
Work stimulation (quadratic term)				.048
Workload (quadratic term)				-.038
Interpersonal conflicts (quadratic term)				.490
Environmental hazards (quadratic term)				.032
Physical demand (quadratic term)				-.001
R_2	.074	.130	.188	.205
ΔR_2		.057	.058*	.017

*Note: * p < .05 (2-tailed). ** p < .01(2-tailed). *** p < .001*

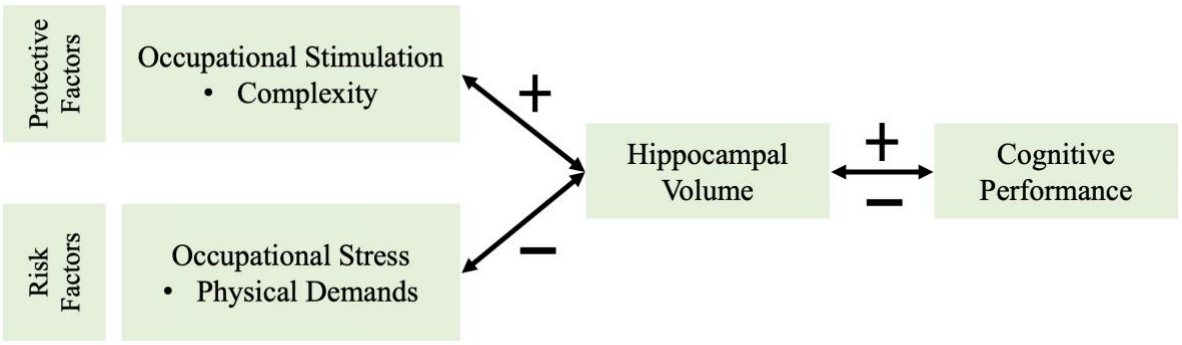

Figure 1. Modified BOSS model; Burzynska, Jiao, & Ganster, 2018

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