THE INFLUENCE OF COGNITIVE RESERVE ON COMPENSATORY BRAIN ACTIVITY

by

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(Under the Direction of Lawrence Sweet)

ABSTRACT

The protective effects of cognitive reserve (CR) in aging have been well-documented, but CR's influence on the association between age-related changes in cognition and neural activation remains unclear. The present study employed a verbal working memory (VWM) paradigm to examine neural response (i.e., activations and deactivations) within the context of two prominent neurocognitive models of aging to determine if neurocompensatory processes support maintenance of cognitive function in 45 healthy older adults, and whether these processes are associated with CR. Results did not support the proposed posterior-anterior (PASA) shift in fMRI brain response, but did reveal reduced hemispheric asymmetry (i.e., HAROLD) of relative deactivations, and an unexpected increase in left-lateralized activations. While CR was not found to influence neurocompensatory processes, VWM performance did, such that only higher performing OAs demonstrated the HAROLD effect of relative deactivations. Findings suggest that deactivations may be particularly sensitive to age-related neurocompensation and warrant further investigation.

INDEX WORDS: Cognitive reserve, Aging, fMRI, Neural compensation, Working memory

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CHAPTER 1

INTRODUCTION

Aging Population

Advancements in health care are increasing the lifespan of individuals worldwide. The number of individuals aged 65 or older is projected to exceed 1.5 billion in 2050 (National Institute on Aging & World Health Organization, 2011). This will be accompanied by new challenges in order to protect the health and safety of older adults (OAs), including increasing financial costs and personal assistance by family members and other caretakers (Alzheimer's Disease International, 2010; ADI). Notably, over and above direct costs of medical and social care provided by community professionals, a considerable portion of this ADI estimate (i.e., 42%) was attributed to the need for informal assistance (e.g., unpaid care by families) with activities of daily living due to cognitive and functional decline. Empirical evidence suggests that naturally aging OAs are at risk for experiencing subtle decrements in the performance of instrumental activities of daily living (IADLs) – that is, abilities necessary for independent living, such as preparing meals, managing money, and taking medications (Burton, Strauss, Hultsch, & Hunter, 2006; Mariani et al., 2008; Schmitter-Edgecombe, Parsey, & Cook, 2011). Therefore, understanding cognitive decline due to the natural aging process can have important real-world implications.

Cognitive Function in Aging

Empirical evidence suggests that various cognitive abilities promote the performance of IADLs, the most important of these are executive functions (EF; Royall, 2007). EFs are diverse but share a common dependence on the function of the prefrontal cortex (PFC; Drag & Bieliasukas, 2009). Age-related decrements are often found on tasks requiring EF processes, such as planning, inhibition, set-shifting, and verbal fluency (Brink & McDowd, 1999; Rodriguez-Aranda & Sundet, 2006; van Hooren et al., 2007; Burgess, 2000; Goldstein, Bernard, Fenwick, & Burgess, 1993; Shallice & Burgess, 1991). Elderkin-Thompson et al. (2008) recently reported that prefrontal structural gray matter volume explained variability in EF performance better than age in an OA sample, suggesting that prefrontal integrity may mediate age-related EF changes. Similarly, Gunning-Dixon and Raz (2003) demonstrated that set-shifting ability correlated negatively with prefrontal volume in OAs. It is important to note that EF decline is not necessarily diffuse EF, as normal aging differentially affects executive subcomponents (Treitz, Heyder, & Daum, 2007).

Working Memory

One area of EF with significant real-world implications is working memory (WM). WM is a system that allows for the storage and manipulation of information for short periods of time (Baddeley, 1986; Baddeley & Hitch, 1974). Therefore, WM processing places large demands on cognitive resources (Babcock & Salthouse, 1990; Bopp & Verhaeghen, 2005), as it requires the successful coordination of a variety of information processing domains in addition to basic storage (e.g., holding a telephone number in short-term memory while simultaneously entering a pin number and then dialing the number). Given the complexity of this higher order cognitive

function, it is not surprising that WM performance declines with increasing age (Bopp & Verhaeghen, 2005; Park et al., 2002; Verhaeghen & Salthouse, 1997). Consistent with this notion, increases in WM task complexity have been shown to magnify relative age-related performance decrements. For example, age differences are more pronounced for a taxing n-Back task than for a simple digit-span task (Dobbs & Rule, 1989). Thus, an OA may be able to write down a simple phone message with ease but may experience more difficulty trying to buffer and calculate prices while grocery shopping. Similarly, WM impairments may also lead to difficulty following long and complex instructions, as OAs may not be able to simultaneously buffer and process this complex information as well as younger adults (YAs).

Several theories have been developed to explain age-related decline in WM. For example, Salthouse (1996) proposed that aging leads to reduced speed of processing, rendering it more difficult to maintain many items in memory at a time. However, it is also possible to link age-related WM decline to a reduced ability to maintain attention focus. In support of this view, there is substantial evidence of reduced inhibition of the processing of distracting or irrelevant information in OAs (Fabiani, Friedman, & Cheng, 1998; Fabiani, Low, Wee, Sable, & Gratton, 2006; Hasher & Zacks, 1988; Hasher, Lustig, & Zacks, 2008). Interestingly, this view of WM decline in aging does not necessarily imply that OAs should show less brain activity relative to YAs during WM tasks.

Functional magnetic resonance imaging (fMRI), a technique that uses magnetic resonance imaging to measure brain activity by measuring changes in the local oxygenation of blood, which in turn reflects the amount of local brain activity, has allowed researchers to investigate changes in brain activity by age. Research literature in this area suggests that there is

an increase in the number of brain regions showing increased activation during the performance of several tasks, including WM tasks (Riecker et al., 2006; Park et al., 2003; for a review, see Reuter-Lorenz & Lustig, 2005), and in many cases findings indicate the occurrence of bilateral activations in OAs when YAs only show unilateral activity (Cabeza, 2002; Cabeza et al., 2004). However, empirical evidence suggests that this may be an oversimplified theory of WM at the neural level. Recent evidence suggests that there may be several age-related brain patterns associated with *graceful aging* on any one task, varying with regard to task-demand, the strategies being employed to solve cognitive problems, or both (Schneider-Garces et al., 2010; Berlingeri, Danelli, Bottini, Sberna, & Paulesu, 2013).

Neural Models of Age-related Cognitive Changes

One prominent model of aging brain function is the hemispheric asymmetry reduction in OAs (HAROLD), which postulates that under similar circumstances, prefrontal activation during cognitive processes tends to be less lateralized in OAs than in YAs (Cabeza, 2002). These patterns of activation have been illustrated using neuroimaging with both simple motor tasks such as button-pressing (Mattay et al., 2002) and also more complex tasks, such as verbal working memory (VWM) and memory retrieval (Backman, Almkvist, Andersson, & Nordberg, 1997; Cabeza et al., 1997; Reuter-Lorenz et al., 2000). The HAROLD model has been well-documented; however, recent evidence suggests that increased bilateral activation observed in prefrontal regions may be specific to higher levels of task demand, and while quantitatively supported in the PFC, the effects may not always be restricted to the PFC (Berlingeri et al., 2013). Thus, in its original version, the HAROLD model appears to capture some, but likely not all of the mechanisms involved in the age-related compensatory brain patterns observed in OAs.

A second consistent neuroimaging finding is of an age-related reduction in occipital and temporal activity coupled with an increase in frontal activity. This posterior-anterior shift, labeled PASA, has also been demonstrated across multiple cognitive functions, including attention (Madden et al., 2002; Cabeza et al., 2004), visuospatial processing (Nyberg et al., 2003; Meulenbroek et al., 2004), working memory (Rypma & D'Esposito, 2000; Grossman et al., 2002), and episodic memory encoding (Anderson et al., 2000; Dennis, Daselaar, & Cabeza, 2005), and episodic memory retrieval (Cabeza et al., 1997; Madden et al., 1999; Grady et al., 2002; Daselaar et al., 2003; Cabeza et al., 2004). In an examination of the validity, function, and generalizability of PASA using episodic retrieval and visual perceptual fMRI paradigms, Davis et al. (2008) reported an age-related reduction in occipital activity coupled with an increase in PFC activity after accounting for differences in difficulty, and a compensatory function of this shift (i.e., negative correlation between occipital reduction and the PFC increase, and a positive correlation between the latter and cognitive performances in OAs). Additionally, the authors reported age-related changes reflecting PASA in the deactivations relative to baseline within regions previously described as part of a "default network," a system including posterior and anterior midline cortices that are often relatively deactivated during task performance compared with a resting baseline. Raichle and collaborators (Raichle et al., 2001; Fair et al., 2007) proposed that these regions support processes active during conscious rest, which must be suppressed to allow for successful cognitive performance. This view is consistent with Davis et al.'s reported findings and suggests that greater anterior medial deactivations in OAs may free up processing resources for engagement of greater PFC activity.

As a result of these models, a general theory of functional compensation has been proposed to account for the observed age-related changes in functional activation. This view suggests that these patterns of activation reflect recruitment of alternate brain regions to counteract neurocognitive decline (Cabeza, 2002; Cabeza et al., 2004). It has been proposed that aging reduces the already limited supply of cognitive processes, producing deficits on demanding cognitive tasks (Craik, 1986). Thus, the aging brain needs to engage additional brain areas to generate the same amount of resources as YAs. For example, it has been suggested that the PASA pattern reflects the recruitment of anterior regions to compensate for processing deficits in more posterior regions (Grady, et al., 1994). Given empirical evidence for the validity of both models across several cognitive domains, as well as evidence that cognitive decline among healthy OAs is diffuse (Drag & Bieliauskas, 2009), it may be that more than one model can explain age-related functional changes in any one cognitive task. Further, several unexplored variables likely account for such age-related functional changes. This may be particularly true for tasks intended to assess higher-order cognitive processes, such as VWM.

Empirical evidence supports the presence of age-related changes in task-independent activity (e.g., in the default mode network; DMN) and related changes in suppression of baseline activity that are associated with effective task-dependent processing. Specifically, healthy aging has been associated with altered patterns of suppression of baseline DMN function (observed as relative deactivations), which may be related to declining resources, difficulties with resource allocation, or both (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Lustig et al., 2003). Another possible explanation arises from a study by Ng et al. (2016), who recently identified longitudinal decline in functional connectivity of the DMN that was further associated

with age-related decline in processing speed. These findings suggested that baseline DMN processing may be altered in OA in ways that may be associated with task-dependent function. Therefore, decline in cognitive performance and associated task-related brain response may be explained, in part, by changes in baseline processing. The link between age and changes in DMN functional connectivity highlights the importance of considering neurocompensatory processes linked to deactivations in healthy OAs. Moreover, OAs have been found to require increased magnitude of deactivations at varying levels of task demand, with magnitude and time course of these deactivations found to be associated with performance changes (Persson, Lustig, Nelson, & Reuter-Lorenz, 2007).

Cognitive Reserve

One factor that may explain differences in age-related neural activity is cognitive reserve (CR). The term "reserve" has been cited as a theoretical framework for explaining individual differences in functional and behavioral responses to neuronal disease or injury (Satz, 1993; Stern, 2002). Specifically, the concept of CR has traditionally been defined as a hypothetical construct that may buffer the effects of brain pathology on clinical outcomes (Satz, Cole, Hardy, & Rassovsky, 2011). Premorbid intelligence, educational attainment, occupational complexity, and leisure activities are believed to be major components of CR and have traditionally served as proxy measures (Whalley, Deary, Appleton, & Star, 2004). CR has been conceptualized as a model that suggests the brain actively attempts to cope with brain pathology by using pre-existing cognitive processes more efficiently or by enlisting compensatory processes (Stern, 2002; Stern, 2009). The vast majority of research on CR has concerned Alzheimer's disease (AD) and nonspecific cognitive impairment (Sachdev & Valenzuela, 2009). The protective

effects of education and occupational attainment on the neurodegenerative process have been well-documented, including a delay in the onset of dementia (Stern, 2009; Valenzuela & Sachdev, 2005), and a buffering of the clinical manifestations of dementia (Hall et al., 2007; Stern, 2002). Pertinent to the current study, empirical evidence also suggests that CR mitigates the effects of aging on cognitive performance, functional abilities, or both in healthy older adults (Sole-Padulles et al., 2009; Bartres-Faz et al., 2009; Corral, Rodriguez, Amenedo, Sanchez, & Diaz, 2006; Duda, Puente, & Miller, 2014). One may infer that if CR mitigates the normal age-related cognitive decline, it may be evident in brain activation patterns. Steffener and Stern (2012) highlight the importance of identifying the neural underpinnings of CR for clinical applications, and on a conceptual level, suggest that CR may moderate the relationship between age and task-related neural activity.

Neural Markers of CR

Although an abundance of epidemiological evidence supports CR's mitigating effect on cognitive and functional outcomes in the face of nonspecific brain pathology, the specific neural markers of CR are less well-defined, particularly in healthy OAs. Nonetheless, identifying the neural substrates of CR is a current topic of interest, particularly among aging researchers. For example, Bosch et al., 2010, provided evidence to suggest that CR is positively correlated with BOLD signal in task-induced activation areas that process speech among patients with MCI and AD, while an inverse correlation was observed among healthy elders. In the same vein, in an fMRI study of visual encoding among healthy OAs and those with MCI and AD, Sole-Padulles et al. (2009) demonstrated that increased brain activity in the pathological groups correlated significantly with higher CR. In comparison, healthy OAs with higher CR exhibited reduced

activity during cognitive processing. Several studies have also shown differential effects of CR on compensatory activation at the network level (Stern et al., 2005; Stern et al., 2008; Bastin et al., 2012).

Results of the aforementioned studies suggest that CR may be identified by quantifying brain activation in specific regions. However, it is difficult to make inferences from the available literature, given that there is a lack of consistency between cognitive processes assessed (e.g., WM, nonverbal recognition, methodology, and group comparisons. Specifically, while group comparisons may help shed light on how CR differentially influences brain activation under cognitive demands, several confounds warrant caution when interpreting results of such studies. For example, the validity BOLD signal comparisons between YAs and OAs have been called into question given the vasculature differences associated with aging (Fabiani, 2012). Additionally, while comparisons of healthy OA to MCI and AD groups provide evidence of relation between CR and compensatory brain activity, results from these group contrasts do not speak to the influence of CR on brain activity among healthy OAs as a unique sample. Therefore, within-group studies of age-related compensatory activity among healthy OAs would provide researchers with opportunities to answer questions about this unique group, and in addition, test the relation between CR and aging models that have been developed to explain different forms of compensatory activation.

Cognitive Reserve as a Moderator

Consistent with CR's influence on age, cognitive performance, and independent daily function, CR may moderate brain activation associated with the cognitive abilities assessed. The aforementioned empirical evidence, while relatively scant and variable in methodology, suggest

that CR may influence age-related compensatory activation in healthy OAs. In order to begin to fill a void in the literature, the present study was intended to test the influence of CR on age-related compensatory activation during a verbal working memory task (VWM). Given that age differences have been shown to be more pronounced for a taxing n-Back task than for a simple digit-span task (Dobbs & Rule, 1989), the present study employed the n-Back task to assess brain activation associated with VWM.

A better understanding of how CR relates to compensatory activation may help us to better identify problem areas in OAs (e.g., less efficient processing of the frontal cortex), and in turn, identify foci for prevention and prognostics in healthy OA, and potentially intervention among clinical populations. Given the rapidly growing aging population, we can expect a vast growth of elder adults affected by neurodegenerative processes, such as AD. Importantly, Katzman et al., 1988, estimated that secondary education delays Alzheimer's for 5 years, and thus, may substantially reduce its prevalence. While AD has been shown to have a strong genetic component, even with late-life onset (Gatz et al., 2006), lifestyle and environmental factors play a strong role in shaping its expression and timing of onset. Thus, more studies that help identify the influence of CR on brain activation in OAs can support the search for optimal ways to intervene (e.g., increase CR), and perhaps eventually aid in the assessment and intervention of neurodegenerative disorders such as AD (Stern, 2013). CR interventions (e.g., secondary education, increases in occupational complexity, physical activity, social engagement, and cognitively stimulating activities) may be a key non-pharmacological approach to preventing this disease (Stern, 2006).

Specific Aims and Corresponding Hypotheses

The present study examined the influence of CR on age-related compensatory activity during a difficult n-Back VWM task, as predicted by HAROLD and PASA models. It was first determined whether HAROLD and PASA effects were observed, and secondary analyses followed in order to examine CR effects on these models.

I. Compensatory activity was examined by quadrant. It was predicted that age would be significantly, positively correlated with reduction in left-hemisphere activation coupled with increased right-hemispheric activation in frontal cortex (i.e., HAROLD: relative bilateralization of response during a lateralized task), and a reduction in posterior activation coupled with increased frontal activation (i.e., PASA). The brain was divided into four quadrants, with compensatory activity measured by averaging brain activity (i.e., mean intensity) by quadrant and calculating left/right and posterior/anterior ratios.

II. The influence of CR on compensatory processes was examined by testing the effects of CR on the relationships between age and the left-right and anterior-posterior ratios. It was predicted that CR would moderate the association between 1) age and bilateralization (i.e., HAROLD neural compensation) and 2) age and anterior-posterior ratio (i.e., PASA) during a left-lateralized VWM fMRI paradigm with well-documented frontal and posterior parietal responses (Smith & Jonides, 1997). Specifically, OAs were expected to exhibit a stronger relationship between age and compensatory activation (i.e., greater bilateralization ratio, posterior-anterior ratio, or both) at lower levels of CR than higher levels of CR. See Figures 1 and 2 for visual illustrations of the moderation models tested.

CHAPTER 2

METHODS

Participants

Participants included 45 healthy, right handed English-speaking older middle-aged to older adults (25 women, age range 53-83, *M* age = 63.78 years, *SD* = 7.99) that served as a control group for a parent cardiac study. Mean level of education was 16.36 (*SD* = 1.96). Participants were recruited from the Providence, RI area. Exclusion criteria included left-hand dominance, uncorrected vision at the time of testing, below 60% performance on the n-Back paradigm, diagnosis of significant heart problems (e.g., surgery, infarct), neurological disease (e.g., multiple sclerosis), low global cognitive function (> 1.5 *SD*s below the sample population on the Mini Mental Status Examination), traumatic brain injury with loss of consciousness, history of substance abuse with subsequent hospitalization, diagnosis of any other current psychiatric illness, or any MRI contraindications (e.g., metal implants). The study was approved by hospital and university Internal Review Boards and conformed to the Helsinki Declaration on human subjects' protection.

Procedures

All participants underwent a telephone screening and informed consent procedures. Participants underwent a three hour neuropsychological assessment, supervised by a licensed clinical psychologist. At a subsequent visit, an MRI assessment was conducted and lasted approximately one hour long. N-Back stimuli were projected onto a screen visible to the

participant while in the scanner. Structural images were acquired at the beginning of the scanning session and n-Back fMRI response was assessed using whole-brain echoplanar BOLD imaging. The concatenated 3D+time datasets were spatially registered and temporally smoothed to minimize movement artifact and improve reliability. Preprocessing of the functional runs also included slice-time correction and registration to correct for head movement. The general linear model (GLM) was used to quantity n-Back for each brain voxel of individual datasets. The resulting individual datasets of brain response to the 2-Back (after controlling the 0-Back active control task and covariates of noninterest, such as observed movement and instructions), expressed as voxel-wise betas, were used to conduct a group level analyses. A region of interest (ROI) procedure was used to assess compensatory activity. ROI activity was averaged by brain quadrant in individually determined clusters of significant activity. HAROLD and PASA models were then assessed by creating laterality indices (LIs) and posterior-anterior (P/A) indices of mean activity.

Measures

Verbal Working Memory Paradigm

The n-Back paradigm was employed to challenge the VWM system. It was comprised of the 2-Back and 0-Back. This 2-Back paradigm is widely used in fMRI research, and therefore has the advantage of a well-described fMRI brain response (e.g., Braver et al., 1997; Owen et al., 2005; Sweet et al., 2008). During the 2-Back, series of consonants were presented visually for 500 ms each, with an interstimulus interval of 2500 ms. During these series participants were asked to make a *yes* or *no* button-press response following each consonant to report whether or not it was the same as the consonant presented two earlier in the series (e.g., w, N, r, **N, R**, Q, **r,**

q, N, W…). Six 45-s series of 15 consonants were presented in two runs. To perform successfully the participant must maintain a demanding cognitive set that includes constant phonemic buffering, subvocal phonemic rehearsal, and executive coordination. Six 0-back control blocks of nine consonants each were presented at the same rate preceding each 2-Back block. Participants responded *yes* when a predetermined target consonant ("H" or "h") appeared and *no* for other consonants using a two-button response. Every consonant block of both conditions contained 33 percent targets in random locations within each series. Capitalization was randomized throughout to encourage verbal encoding. Overall, six 0-Back control blocks alternated with six 2-Back blocks. Two 27-s series of resting fixation blocks, in which participants were asked to look at a "+" presented in the middle of the screen, were presented between the 0-Back/2-Back cycles (i.e., twice per imaging run). The 0-Back/2-Back cycles were counterbalanced across imaging runs. See Figure 3 for an illustration of the paradigm.

Cognitive Reserve

A composite variable of formal years of education and premorbid IQ served as a measure of CR. The rationale to create a composite variable was supported by empirical evidence of unique contributions from multiple proxies of CR. Given that years of education may be influenced by many sociological and cultural influences unrelated to innate intelligence or brain health (Knopman, 2011; Manly, Schupf, Tang, & Stern, 2005; Manly, Touradji, Tang, & Stern, 2003), investigators have suggested that literacy may be a more accurate representation of CR than educational attainment (Manly et al., 2005, 2003). In contrast, numerous findings suggest factors other than education (e.g., innate intelligence, occupational attainment, and leisure

activities) may contribute independently to cognitive reserve (Stern, Tang, Denaro, & Mayeux, 1995; Stern, 2009).

Premorbid IQ was derived from the standard score of the Wechsler Test of Adult Reading (WTAR; Holdnack, 2001) and treated as a continuous variable. Each measure was converted to normally distributed z-scores and the average of all z-scores was computed in order to comprise a composite score for our proxy of CR. Formal years of education was determined for each participant via self-report and treated as a continuous variable in the analyses. Following the procedures of Siedlecki et al., (2009), to quantify formal years of education attainment, 20 was the highest level representing a doctoral degree, 18 represented a master's degree, 16 represented a bachelor's degree, 14 represented an associate's degree, and 12 was assigned for a high-school degree or General Educational Development certificate (GED). Additionally, each year for formal education, regardless of whether it was or was not a degree-granting year, was counted as a formal year of education. For example, a high-school graduate who complete one year of college would be considered to have completed 13 years of education. The maximum number of years of education was limited to 20.

Cronbach's alpha was calculated in order to ensure internal consistency of the composite score derived from the two individual measures. Results indicated a value ($\alpha = 0.38$) considerably lower than the appropriate level of internal consistency recommended (i.e., $\alpha = 0.80$; Sijtsma, 2009; Tavakol & Dennick, 2011). Relative to the multiple proxies of CR discussed in the literature, education has been a particularly well-documented protective factor against cognitive decline associated with healthy aging (Albert et al., 1995; Butler et al., 1996; Chodosh et al., 2002; Christensen et al., 1997; Colsher & Wallace, 1991; Farmer et al., 1995;

Lyketsos et al., 1999; Snowdon et al., 1989). Additionally, results of a recent study (Jefferson et al., 2011) that utilized path analysis to explore late-life factors on cognition suggest that education may be the strongest among the tested proxies of CR (i.e., early-, mid-, and late-life participation in cognitive activities; early- and late-life socioeconomic status, SES; and reading ability). Therefore, given the population of interest in the present study (i.e., community-dwelling older adults), formal education was thus utilized as the single proxy of CR.

Neuroimaging

Data acquisition

Whole-brain echoplanar fMRI was conducted using a Siemen's TIM Trio 3 tesla scanner (TR = 2500 ms, TE = 28 ms, FOV = 192^2, matrix size = 64^2, in 42 3-mm-thick axial slices). This procedure yielded 116 whole-brain volumes for each of the two 4:48-min imaging runs, yielding a spatial resolution of $3mm^3$ per voxel. Whole-brain high-resolution T1 images were also acquired in the sagittal plane for anatomical reference (TR = 1900 ms, TE = 2.98 ms, FOV = 256^2 mm, matrix size 256^2). The n-Back was presented using E-prime (Psychology Software Tools, Sharpsburg, USA) and back-projected onto a screen visible to the participant via a mirror mounted to the head coil.

Data processing

FMRI dataset processing and statistical analyses were performed with the Analysis of Functional NeuroImages software (AFNI; Cox, 1996). The concatenated 3D+time datasets were spatially registered and temporally smoothed to minimize movement artifact and improve reliability. Preprocessing of the functional runs included slice-time correction and registration of each volume to the third volume of the first imaging run to correct for head movement. Data

from participants with head movement of > 3.0 mm (one voxel size) in any direction were omitted from analyses. Individual anatomical images were aligned to the volume-registered functional run, skull-stripped, and then transformed into Talairach space. The functional runs in native space were then aligned to the anatomical image in Talairach space using the concatenated transformation matrices from the volume registration, anatomical to functional alignment, and anatomical transformation into standard space. A 5-mm full-width Gaussian filter was applied and the raw time-series was scaled to a mean of 100 to enable interpretation as a percent signal change from baseline and facilitate comparison across participants.

Quantification of individual effects

The general linear model (GLM) was used to quantify condition-specific activity for each brain voxel of individual datasets. To accomplish this, a regression of the temporal pattern of 2-Back presentation, 0-Back control task presentation, and covariates (i.e., instruction screens, observed movement, linear drift) were performed using BOLD signal over time as the dependent variable. A general linear contrast was added to the GLM to enable exploration of the direct effects of the 2-Back compared to the 0-Back. Thus, three resulting individual activation maps reflected the unique effects of each condition (i.e., 2-Back VWM and 0-Back active control task) compared to resting baseline, and a follow-up general linear test (GLT) to quantify the 2-Back effects specifically relative to 0-Back control task. The resulting individual datasets of significant brain response to the 2-Back, expressed as voxel-wise betas, were used to conduct a group level analysis using their mean betas across significantly active clusters per brain quadrant as the dependent measure of brain activity. This method was intended to provide a uniform

measure of mean activity per quadrant across participants and conditions suitable for parametric statistical analyses.

Computation of the GLM (2-Back vs rest) allowed for analysis of 2-Back effects relative to a resting (i.e., fixation) baseline *over and above* mean intensity effects associated with 0-Back task completion. In other words, the "GLM 2-Back effects" (referred to hereafter), relative to a resting baseline, after parceling out unique effects of the 0-Back active control condition. This enabled the use of a resting baseline, which is ideal for examination of task-independent deactivations. Application of a general linear contrast (e.g., active control condition subtracted from an activate task condition) has been commonly employed in the literature as a means of isolating functional brain patterns associated with specific cognitive processes. Therefore, the "GLT 2-Back effects" (referred to hereafter) in order to maintain consistency with prior literature.

Results of GLM procedures to quantify individual activation patterns at the voxel level were first thresholded using a two-tailed $p < .05$, corrected for multiple comparisons using AFNI's false discovery rate (FDR) procedure (Cox, 1996). The mean of averaged 2-Back associated LI (i.e., left/right) values computed for the sample were not normally distributed (i.e., skewness and kurtosis values exceeding 1) and transformation options (e.g., z-scores, log transformation) did not resolve this issue. However, the application of a more stringent two-tailed $p < .01$ threshold, FDR-corrected for multiple comparisons resulted in a normal distribution across participants. Therefore, subsequent analyses of HAROLD and PASA effects were conducted using quantification of individual effects using this more stringent voxel threshold.

Group level whole-brain voxel-wise analysis and validation of brain response

Qualitative procedures were conducted to examine the validity of brain activation patterns exhibited by the sample, and subsequently used to examine the hypotheses. These were accomplished by examining the overlap between clusters of significant n-Back response exhibited by our sample and prior n-Back literature (e.g., Smith & Jonides, 1997; Owen et al., 2005).

A priori hypotheses were then tested by examining brain response patterns at the individual level, quantifying the mean intensities of individuals' relative activation and deactivation clusters by quadrant, and then calculating L/R and A/P ratios for use in determining HAROLD and PASA effects by age. As noted above, in order to identify clusters of significant brain response per individual, results of the voxel-wise analyses were thresholded using a two-tailed alpha of .01 and corrected for multiple comparisons using AFNI's false discovery rate procedure (Cox, 1996).

Definition of quadrants

In order to test hypotheses it was necessary to quantify significant task-related effects by brain quadrant. To accomplish this, the brain was divided into four quadrants based on (a) left or right hemisphere (i.e., relative to Talairach coordinate x-plane = 0), and (b) anterior or posterior – using a coronal plane at the anterior commissure (i.e., relative to Talairach coordinate y-plane = 0).

Definition of the variables used in hypothesis testing

HAROLD

Laterality indices (LIs), defined as left relative to right (left/right) frontal quadrant response to the n-Back paradigm, were calculated using mean intensity effects (betas) in individually determined clusters of significant brain response for each quadrant. That is, significant voxel-wise intensity effects were averaged by quadrant within each individual's "functionally defined ROIs" (i.e., voxels in clusters exhibiting significant 2-Back response in left and right frontal quadrants). Consistent with prior literature (Baciu et al., 2005; Yuan et al., 2006; Deblaere et al., 2004), an LI was calculated by subtracting intensity effects within the right frontal quadrant from intensity effects within the left frontal quadrant, then dividing this value by the average of mean activity across the two frontal quadrants (i.e., left frontal – right frontal / (left + right frontal). This process was conducted separately for relative activation and relative deactivation.

PASA

Posterior-anterior indices, defined as posterior/anterior brain response, was calculated using mean intensity effects (betas) within individually determined "functional ROIs" (i.e., clusters of significant brain response to the 2-Back paradigm by quadrant). The significance threshold was a two tailed alpha level of .01 and FDR corrected for multiple comparisons. Intensity effects were averaged across the two frontal quadrants and the two posterior quadrants. The P/A ratio was calculated by dividing mean intensity effects within the posterior quadrants by intensity effects within the anterior quadrants, then dividing this value by the average of mean intensity effects across all four quadrants (i.e., (left posterior + right posterior) – (left frontal +

right frontal) / (left posterior + right posterior + left frontal + right frontal). This procedure was conducted separately for relative activation and relative deactivations.

Analytic plan

Assessing Laterality of n-Back-Related Brain Activity

Hemispheric dominance has been commonly determined by the size of the LI (Baciu et al., 2005; Yuan et al., 2006; Deblaere et al., 2004). Following the criteria adopted Yuan et al., 2006, an LI threshold of .10, representative of 10 percent greater left relative to right hemispheric activity was considered evidence of lateralization. LIs specific to activations and deactivations were examined separately. As reported elsewhere (Smith & Jonides, 1997), it was expected that brain activity elicited during the 2-Back VWM task would be left-lateralized (i.e., LI > .10 for activations; LI < -.10 for deactivations).

Assessing HAROLD and PASA

Support for the HAROLD model was assessed by performing a bivariate correlation analysis of age and the LI between the two frontal quadrants. Similarly, support for the PASA model was assessed by performing a bivariate correlation analysis of age and the P/A ratio.

Multiple Regression and Moderation Analyses

The HAROLD and PASA models were expected to be supported due to consistent prior literature reporting medium to large effect sizes (Davis et al., 2008; Cabeza et al., 2004). Expecting the HAROLD and PASA models to be supported, the second aim was to determine whether the relations between age and compensatory activation (i.e., of LI and P/A indices) were moderated by CR.

Before conducting moderation analyses, assumptions of multiple linear regression were examined, including homoscedasticity, independence of residuals and normality of residuals (Cohen, Cohen, West, & Aiken, 2003). Multicollinearity between the independent variable and moderator were reduced through the use of centering (Aiken & West, 1991).

For moderation analyses, the publicly-available PROCESS SPSS macro plug-in (http://afhayes.com/introduction-to-mediation-moderation-and-conditional-process-analysis.html; Hayes, 2012) was applied to examine the data within a multiple regression framework. In PROCESS, moderation is present when the interaction term between the predictor (age) and the moderator variable (CR) is significant and the confidence interval does not include zero. Therefore, a moderator variable should impact the direction and/or strength of the relations between the independent and dependent variables (Baron & Kenny, 1986). PROCESS allows the researcher to probe an interaction in several ways, all of which require fewer calculations than would be necessary in most other regression approaches (Hayes, 2012). For the present study, the interactions were visually probed in order to examine the nature of any moderation effects by examining conditional effects (i.e. simple slopes) at low (-1 *SD* below the mean) and high (+1 *SD* above the mean) levels of CR.

Power Analyses

Power analyses were conducted with the G*Power software package (Erdfelder, Faul, & Buchner, 1996) to ensure that the current sample size was adequate to detect the hypothesized effects. Previous studies have reported medium-to-large HAROLD and PASA effect sizes (Davis et al., 2008; Cabeza et al., 2004). Power analyses indicated that a total sample of 37 participants would be needed to detect the expected medium effects (i.e., r = .40) with .70 power using a two-

tailed) alpha of .05. Regarding the second aim of the current study, the projected sample size of 37 participants, power of .70, and one-tailed alpha = .05 allow for the detection of a medium interaction effect size (R-squared change = .20).

CHAPTER 3

RESULTS

Preliminary Analyses

Preliminary and primary data analyses were conducted using the Statistical Package for Social Sciences (SPSS 21.0 for Windows, SPSS, Chicago, IL). Demographic characteristics and cognitive performance are displayed in Table 1. The study sample was comprised of older adults with above average intellectual functioning and educational attainment. WM performance accuracy was consistent with prior 2-Back literature (Smith & Jonides, 1997; Braver et al., 1997; Sweet et al., 2008).

CR Composite Variable

Cronbach's alpha was calculated in order to ensure internal consistency of the composite score derived from the two individual measures (i.e., education and WTAR). Results indicated a value ($\alpha = 0.38$) considerably lower than the appropriate level of internal consistency recommended (i.e., $\alpha = 0.80$; Sijtsma, 2009; Tavakol & Dennick, 2011). Relative to the multiple proxies of CR discussed in the literature, education has been a particularly well-documented protective factor against cognitive decline associated with healthy aging (Albert et al., 1995; Butler et al., 1996; Chodosh et al., 2002; Christensen et al., 1997; Colsher & Wallace, 1991; Farmer et al., 1995; Lyketsos et al., 1999; Snowdon et al., 1989). Therefore, given the population of interest in the present study (i.e., community-dwelling older adults), formal education was thus utilized as the single proxy of CR. Multiple regression and moderation analyses were also

conducted with WTAR as a single proxy of CR and achieved the same results as education as a single proxy of CR.

fMRI Response

Brain response patterns associated with the 2-Back are listed in Tables 2-3 and Figures 4-5. Results of these whole-brain voxelwise analyses revealed regions of activation consistent with prior literature, including the bilateral dorsolateral prefrontal cortex, medial frontal gyrus, posterior parietal cortices, anterior insula, thalamus, and cerebellum (Owen et al., 2005; Smith & Jonides, 1995; Sweet et al., 2008). Relative deactivations were also consistent with prior literature and overlapped substantially with regions associated with the DMN (Sweet, et al., 2008; Buckner et al., 2008). Qualitatively, GLM 2-Back deactivations relative to rest were more robust, as expected, and consistent with using rest as a baseline (Buckner et al., 2005).

Assessment of Laterality during the n-Back Paradigm

Following quantification of significant brain response, mean intensity effects were summarized by quadrant for both activations and deactivations (Tables 6-7). Mean intensity effects and LI and P/A indices for 2-Back (controlling 0-Back and other covariates) are reported in Table 5 by activation and relative deactivation. These are reported for the 2-Back versus 0-Back GLT in Table 6. 2-Back associated LIs yielded the expected left-lateralization for both activations (M = .11; SD = .20) and deactivations (M = .11; SD = .21). LIs related to the 2-Back versus 0-Back GLT contrast yielded mixed results. Task-associated activation did not yield the expected left lateralization (LI M = .05; SD = .26). However, the LI was indicative of left-lateralized relative deactivation (LI M = .23; SD = .22), such that the left hemisphere exhibited greater deactivation.

Primary Analyses

Tests of Hypothesis 1: HAROLD & PASA effects

Bivariate correlation analyses between age and the P/A ratios were not significant for GLM (i.e., 2-Back versus resting baseline after controlling 0-Back) or GLT (i.e., the direct 2-Back versus 0-Back contrast) derived 2-Back activation or relative deactivation effects.

Bivariate correlations between age and the LI of GLM 2-Back effects (i.e., versus resting baseline, after controlling variance associated with the 0-Back control task) were conducted in order to examine HAROLD effects. Results were significant for both activations ($r = .31$, $p = .04$) and deactivations ($r = -.30$, $p = .05$), such that increasing age was significantly and positively associated with the activation LI and negatively associated with the deactivation LI (Table 6). Bivariate correlations between age and LIs reflecting 2-Back versus 0-Back GLT effects were not significant (Table 9).

The significant GLM 2-Back (versus rest after controlling 0-Back) results are presented in Figure 6 in graphic form for illustrative purposes. Differences in mean intensity effects between LI activity patterns were computed using independent samples t-tests. A median split of age (median = 63 years) was used to divide the sample into two groups: old-old (n = 23) and young-old (n = 22). Results revealed significant differences specific to left-lateralized deactivations ($t = 2.40$; $p = .02$), such that young-old ($M = .61$; $SD = .41$) but not old-old ($M = .47$; $SD = .36$) participants evidenced positive and significant hemispheric asymmetry. Importantly, these results are presented in this format for the purpose of aiding visualization of the significant findings presented in the previous paragraph.

Tests of Hypothesis II: Hierarchical Multiple Regression and Moderation Analyses

Hierarchical multiple regression and moderation analyses were conducted to test the influence of CR on HAROLD and PASA effects. For each multiple regression analysis, age was entered in Step 1, and CR (i.e., education) was entered in Step 2. The age x education interaction term was entered in Step 3 for each subsequent moderation analysis.

Given the potential confounding effects of differing performance level across participants, this moderation procedure was repeated to examine the influence of 2-Back performance accuracy on the significant HAROLD effects. Performance was calculated for each participant using the following formula: (number of correct hits + correct rejections)/ total number of trials.

GLM 2-Back effects

Consistent with the lack of evidence supporting PASA effects, neither age nor CR accounted for a significant portion of unique variance in any P/A index, and CR did not influence the relation between age and P/A indices (Table 10). Age accounted for a significant portion of variance in LI for both activations ($B = .01$; $SE_B = .00$; $p < .05$) and deactivations ($B = -.01$; $SE_B = .00$; $p < .05$), but CR did not account for significant variance in LI (see Table 12).

Exploratory Analyses

In exploratory analyses of n-Back performance as a moderator specific to activations, neither age (total $R^2 = .10$; $B = .01$; $p = .07$) nor 2-Back performance ($B < -.01$; $p = .64$) accounted for unique variance in LI. Neither CR (total $R^2 = .10$; $\Delta R^2 < .01$; $B = < -.01$; $p = .91$) nor 2-Back (total $R^2 = .10$; $\Delta R^2 < .01$; $B = < -.01$; $p = .91$) were found to moderate the relation between age and LI (Table 14). In contrast, for deactivations, age significantly and negatively

predicted LI (total R^2 = .26; B = .01; p = .03) and representative of a HAROLD effect (i.e., increasing age associated with reduced frontal asymmetry). In addition, 2-Back performance (B = .01; p = .05) significantly and positively predicted LI. Interestingly, results of moderation analysis revealed 2-Back performance as a significant and negative moderator between age and LI (total R^2 = .26; ΔR^2 = .08; B < -.01; p = .04), suggesting that better 2-Back performance is associated with a stronger relationship between age and LI. These hierarchical multiple regression and moderation results are presented in Table14.

Given evidence of an interaction between age and 2-Back performance, simple slopes analyses were conducted by estimating the conditional effect of age at specific values of 2-Back performance (in this case, ±1 SD from the sample mean, or -9.70 and 9.70, respectively) and tested whether the slopes were statistically significant from zero by a null hypothesis test (for details of this method, see Hayes, 2013). Results of the analyses revealed a significant association between age and LI, with age significantly related to LI for higher levels of 2-Back performance (B = -.02, p = .01) but not significantly related to LI for lower levels (B < -.01, p = .88). In order words, high 2-Back performers evidenced a stronger negative relationship between age and LI, or HAROLD effects. A plot of the simple slopes analyses is presented in Figure 7.

GLT 2-Back effects

Age did not account for a significant portion of variance in LI for both activations (B = .01; SE_B = .00; p < .05) and deactivations (B = -.01; SE_B = .00; p < .05), and CR did not account for significant variance in LI (see Table 13).

While age did not significantly account for unique variance in LI of activation (total R2 = .14; B = .01; p = .45), 2-Back performance did (B = .01; p = .02). However, neither CR (total R^2

= .02; ΔR^2 = .01; B = < -.01; p = .48) nor 2-Back (total R^2 = 14; ΔR^2 <.01; B = < -.01; p = .68) were found to moderate the relation between age and LI. For deactivations, neither age (total R^2 = .08; B < .01; p = .33) nor 2-Back performance (B = .01; p = .15) significantly predicted LI, and neither CR (total R^2 = .09; ΔR^2 = .04; B < .01; p = .19) nor 2-Back performance (total R^2 = .08; ΔR^2 < .01; B < .01; p = .80) were not found to moderate the relation between age and LI. These hierarchical multiple regression and moderation results are presented in Tables 15.

CHAPTER 4

DISCUSSION

The present study examined the influence of CR on age-related compensatory activity during a difficult n-Back VWM paradigm, as predicted by HAROLD and PASA models. It was first determined whether HAROLD and PASA effects were present (Hypothesis 1), and then CR effects on these models were examined (Hypothesis 2). This was the first simultaneous examination of multiple compensatory processes within a sample of community-dwelling OAs. Findings revealed some evidence of left-lateralization of fMRI brain response (i.e., effects for both activations and deactivations) and mixed support for Hypothesis 1. Specifically, while PASA was not supported in any of the analyses, there was evidence of a HAROLD effect such that the deactivation LI was associated with age. Hypothesis 2 was not directly supported. Specifically, CR moderation effects were not identified; however, 2-Back performance accuracy moderated the deactivation LI, suggesting that a) education, as an individual proxy of CR, may not explain variance in neurocompensation processes, and b) deactivations may be particularly sensitive to the aging process.

Hypotheses were tested using two quantification methods that have yielded complementary information in prior literature. The GLM 2-Back quantification (i.e., 2-Back versus rest after controlling 0-Back) provided an examination of fMRI brain response patterns using a passive baseline condition conducive to identification of deactivations, or suppression of baseline functioning. This was the primary approach, given the diffuse nature of age-related

cognitive decline across domains (Drag & Bieliauskas, 2009) and observation of age-related task-independent alterations in fMRI brain response patterns (e.g., relative deactivations; see Cabeza et al., 2004 for review)GLM 2-Back analysis provided an opportunity to examine neurocompensatory processes relative to both activations and deactivations after parceling out 0-Back effects associated with basic cognitive functions such as motor and attentional processing. Although the GLM method is better designed to examine activation and deactivation, and was thus a more effective method for tests of our hypotheses, the GLT results are also interpreted for comprehensiveness and integration into prior literature.

GLM 2-Back Effects

The GLM-derived activation LI supports the assumption of left-lateralized fMRI brain response associated with the 2-Back task and is consistent with previous findings (Owen et al., 2005; Smith & Jonides, 1997). Further, the deactivation LI also supported left-lateralization, extending prior literature to support the notion of lateralization of deactivations in task independent regions such as the default network.

Employing the GLM was also useful for examining moderation effects. GLM findings support some aspects of Hypothesis I (i.e., HAROLD relative to deactivation), but no support for Hypothesis II (i.e., CR as a moderator of the relation between LI and age). However, 2-Back performance was found to moderate the relation between age and the deactivation LI, indicative of a different compensatory process benefiting cognitive function.

Interestingly, results of the significant and *positive* correlation between age and LI, specific to activations, suggests that increased left-lateralized activity supported OAs maintenance of cognitive functioning. While this finding refutes the HAROLD model, it is

consistent with the compensation-related utilization of neural circuits hypothesis (CRUNCH), which posits that processing inefficiencies cause the aging brain to recruit more neural resources (e.g., "overactivation") in order to achieve computational output comparable to that of a younger brain (Reuter-Lorenz & Cappell, 2008). The compensation hypothesis assumes that overactive sites in OA brains that reflect greater effort than the corresponding regions in their younger counterparts in order to make up for declining efficiency or processing deficiencies. Age-related, region-specific overactivation is a well-documented finding for a wide range of processes, including executive functions, motor control, episodic, autobiographical and working memory (see Reuter-Lorenz & Lustig, 2005, for review). Therefore, left-lateralized overactivation identified among the present sample appears to be consistent with the CRUNCH model.

Uncertainty regarding the function of overactivations, however, has led to increased interest in cognitive performance correlates. For example, overactivation among OAs has been linked to both reduced cognitive performance (Johnson, Mitchell, Raye, & Green, 2004; Thomsen et al., 2004; Logan, Sandders, Snyder, Morris, & Buckner, 2002; Park et al., 2004; Milham et al., 2002), as well as maintained or improved performance (Persson et al., 2004; Gutchess et al., 2005; Rossi et al., 2004; Grady, McIntosh, & Craik, 2003), that have been interpreted to reflect impairment versus compensation, respectively (see Reuter-Lorenz & Lustig, 2005 for review). In the present study, 2-Back accuracy was not found to moderate the relation between age and LI for activations, suggesting that increased left-lateralized activity did not result in improved performance. That is, higher performing OAs did not differ from lower performing OAs with respect to the degree of overactivation. However, empirical evidence of maintained performance suggests that the identified overactivation may reflect maintenance of

cognitive function. While higher performing OAs did not evince a greater degree of overactivation, lower performing OAs also did not demonstrate a greater degree of overactivation (see Table 6). Therefore, it is plausible that the lower performing OAs maintained previous levels of cognitive function prior to age-related decline via increased left-lateralized activation.

GLT 2-Back Effects

The GLT method of quantifying 2-Back effects was not as informative as the GLM method. Relative to predefined thresholds used to assess laterality (see Seghier, 2008 for review), assessment of LIs specific to VWM task-associated activation did not yield expected left-lateralization. However, the LI was indicative of left-lateralized relative deactivation, such that the left hemisphere exhibited 23% greater deactivation relative to the right hemisphere. Lack of support for HAROLD and PASA effects specific to GLT-derived activations and deactivations suggest that neurocompensation may be related to a range of cognitive processes, particularly those active at rest (e.g., DMN), and not necessarily specific to VWM.

Extension of HAROLD to Deactivations

Results of the significant and negative correlation between age and the deactivation LI, coupled with maintained 2-Back performance (i.e., > 60% for each participant) suggests that reduced asymmetry of deactivations supported OAs' maintenance or improvement in cognitive functioning. Reduced asymmetry of brain activation is consistent with the HAROLD model. However, in extending previous findings to deactivations, and more specifically, via a within-group fMRI study of community-dwelling OAs, we have provided evidence of a novel HAROLD finding. Interestingly, a growing body of literature supports the presence of age-

related changes in the deactivation (e.g., decreases relative to baseline) of task-independent regions that are thought to be associated with cognitive control (Hafkemeijer, van der Grond, & Rombouts, 2012; Sambataro et al., 2010). Furthermore, age-related changes in deactivation have been found to be associated with maintenance of cognitive performance (Persson et al., 2007; Tomasi, Ernst, Caparelli, & Chang, 2006; Anticevic, Repovs, Shulman, & Barch, 2010) and cognitive reserve (Bosch et al., 2010; Tucker & Stern, 2011), consistent with theory of compensatory processes. Collectively, results of the present study provide further evidence that deactivations within task-independent regions may be particularly important in maintenance of cognitive performance in the face of age-related decline.

In contrast to findings specific to activations, n-Back accuracy was found to moderate the relation between age and LI for deactivations, suggesting that reduced asymmetry of deactivations resulted in improved cognitive function. Results of simple slopes analyses revealed that higher performing OAs demonstrated an increased reduction of asymmetry specific to deactivations while lower performing OAs did not (see Figure 4). This finding provides further evidence of age-related sensitivity to changes in deactivations. Evidence of improved cognitive function associated reduced asymmetry is consistent with the expectation that compensatory processes aide in OAs ability to maintain or improve cognitive function.

Age-Related Changes in Deactivation

Findings of the present study support the notion that deactivations are sensitive to the aging process, lateralized similarly to task-induced activations, and associated with successful task performance. Task-induced deactivations, or less activity during an experimental task than during a passive baseline condition, have become the target of much investigation (Hansen et al.,

2014; Binder, 2012; Gilbert, Bird, Frith, & Burgess, 2012). Deactivations appear to occur when participants switch from unconstrained processes (e.g., attending to external environmental stimuli, monitoring one's own internal state and emotion, autobiographical/episodic memory processing), and the components of the default network have been shown to be stable across tasks (Persson et al., 2007). However, evidence suggests deactivations are sensitive to the normal aging process (Grady et al., 2006; Rombouts, Barkhof, Goekoop, Stam & Sheltens, 2005; Lustig et al., 2003). For example, OAs demonstrate reduced magnitude of deactivations, slower default network processing, sensitivity to cognitive load, and a relation to task performance (Persson et al., 2007). Given evidence that deactivations reflect a reallocation of resources away from default network processing and toward the demands of the experimental task (McKiernan et al., 2003; Daselaar, Prince, & Cabeza, 2004), alterations in suppression of the default network may be associated with compensatory processes similarly to task-specific alterations supporting cognitive performance (Cabeza, 2002; 2004).

Neurocompensatory Processes

Although PASA effects were not identified, and CR did not significantly moderate the relation between age and LI and P/A indices, results revealed neurocompensatory processes specific to both deactivations and activations. Specifically, participants evidenced an age-related increase in left-frontal activations suggestive of compensation, as well as a reduction in asymmetry of deactivations consistent with the HAROLD model. Moreover, compensatory brain response was noted such that reduced asymmetry of deactivations was moderated by increased 2-Back accuracy, indicating that deactivations relative to the resting state baseline may be particularly sensitive to age-related compensation.

Compensatory brain response patterns consistent with the HAROLD and PASA models have been consistently identified via direct contrasts of brain response patterns between OAs and YAs (Cabeza, 2002; Mattay et al., 2002; Backman et al., 1997; Reuter-Lorenz et al., 2000; Madden et al., 2002; Cabeza et al., 2004, 1997; Nyberg et al., 2003; Rypma et al., 2004; Davis et al., 2008). The present study is the first within-group examination of compensatory brain activity among OAs during the performance of a VWM task. A lack of support for PASA and some HAROLD effects may be related to inhomogeneity of variance across the lifespan. That is, healthy older adults (i.e., over age 50) may exhibit less variability in fMRI brain response patterns in a within-group design than would be identified in a direct contrast with healthy young adults.

While the HAROLD and PASA models have been commonly studied in OAs, empirical evidence supports the presence of other compensatory processes that may support maintenance of cognitive abilities in OAs. For example, differences in capacity, or the degree to which a task-related brain network is maximally recruited to keep performing a task, even in the face of increasing demands, has been associated with maintenance of cognitive abilities (Bosch et al., 2010). At the level of brain networks, the compensation-related utilization of neural circuits hypothesis (CRUNCH) theory states that, as a task becomes more difficult, a network will be recruited to an increasing degree (Reuter-Lorenz & Cappell, 2008). In the same vein, empirical evidence has supported the scaffolding theory of aging and cognition (STAC), which posits that recruitment of additional neural circuits or networks occurs when the primary networks have become inefficient or damaged due to age or pathology (Park & Reuter-Lorenz, 2009). Thus, one

or more broader theories of compensation may better explain successful maintenance of VWM in the face of age-related decline.

Absence of the moderating effect of CR suggests that other factors may explain differences in fMRI brain response patterns and VWM performance within this population. For example, according to the concept of brain reserve capacity (BRC), individuals may differ in their reserve capacity depending upon individual differences in brain structure (e.g., greater brain volume, larger neuronal numbers, increasing dendritic proliferation, or greater synaptic density). Although the relationship between CR and BRC are not yet well understood, early evidence suggests CR indices may be related to differences in underlying structural brain differences (Foubert-Samier et al., 2012). For example, additive (i.e., BRC + CR) or interactive (i.e., BRC x CR) effects may account for individual differences in age-brain activity relation.

Utilizing a composite proxy of CR may also be a more effective method for quantifying the CR construct in detection of the potential influence of CR on compensatory processes. Given that years of education may be influenced by many sociological and cultural influences unrelated to innate intelligence or brain health (Knopman, 2011; Manly et al., 2005; Manly, Touradji et al., 2003), investigators have suggested that literacy may be a more accurate representation of CR than educational attainment (Manly et al., 2005, 2003). In contrast, numerous findings suggest factors other than education (e.g., innate intelligence, occupational attainment, and leisure activities) may contribute independently to reserve (Stern et al., 1995; Stern, 2009). Therefore, development of more comprehensive (e.g., latent variable integrating multiple proxies of CR) or novel approaches to operationalizing CR (Zahodne et al., 2013) may be more effective future alternatives.

Limitations

Few studies have investigated HAROLD and PASA effects specific to WM among healthy OAs, and all were older positron emission tomography (PET) studies. Prior literature has also focused almost exclusively on group differences (i.e., YA versus OA) in HAROLD and PASA effects specific to task-dependent activations (i.e., six of seven studies) associated with WM. Interpretation of our findings is therefore limited by comparison to prior studies, particularly those utilizing fMRI WM paradigms.

The sample of the present study was relatively young with respect to the aging literature (range = 53 to 83 years; mean = 63.78, SD = 7.99), as researchers often sample OA populations from 65 years and beyond due to general trends in age-related cognitive decline. Interpretation of study findings are also limited by a relatively small sample size (i.e., not adequately powered to detect moderation effects within the small – moderate range). The majority of the sample were also intelligent (WTAR range = 96 – 119, mean = 111.53, SD = 6.4), well-educated (range = 12-21 years; mean = 16.36; SD = 1.96) and of Caucasian ethnicity (96%), which poses potential problems with generalizability.

Lastly, our attempt to develop a composite variable of CR was ineffective due to multicollinearity between years of educational attainment and premorbid IQ. Issues of conceptualization and measurement in research on CR have been heavily debated (Barulli & Stern, 2013; Jones et al., 2011; Knopman, 2011) and highlight the challenges of effectively capturing the construct. For example, direct measures of the hypothetical construct are not available. *In vivo* measures of neuronal pathology are also not widely available, further challenging researchers to develop and test models of CR that involve a risk factor (e.g., injury

or pathology), a moderator (e.g., reserve), and an outcome (e.g., performance or clinical status; Jones et al., 2011).

Future Directions

As the first investigation of multiple age-related neurocompensatory processes utilizing a within-group experimental design, findings of the current study warrant replication. Given our identification of dual neurocompensatory processes (i.e., HAROLD effect relative to deactivations and increasing left-lateralization of activations) using a VWM paradigm, future investigations may also benefit from consideration of newer models of neurocompensation such as CRUNCH and STAC-R. Consistent with the CRUNCH model, results of the present study suggest that multiple compensatory processes may support cognitive function in old age.

Coupled with evidence of age-related changes in deactivations, results of the present study also highlight the importance of examining neurocompensatory processes relative to both task-dependent and task-independent brain responses. Evidence of HAROLD effects relative to deactivations suggest that baseline DMN processing may be altered in OAs and also associated with effective task-dependent function. Therefore, decline in cognitive performance and associated task-related brain response may be explained, in part, by changes in baseline processing. The link between age-related changes in DMN functional connectivity highlights the importance of considering neurocompensatory processes linked to deactivations in healthy OAs. There may be additive or interactive effects that account for neurocompensatory processes as well, which would be consistent with evidence of competition between task-dependent (e.g., VWM) and task-independent (e.g., DMN) brain activity (Kelly et al., 2008).

Empirical evidence suggests that numerous factors independently contribute to CR (Stern et al., 2009), some of which (i.e., education) may be influenced by sociological and cultural influences unrelated to innate intelligence or brain health (Knopman, 2011; Manly et al., 2005; Manly, Touradji et al., 2003). Therefore, development of more comprehensive (e.g., latent variable integrating multiple proxies of CR) or novel approaches to operationalizing CR (Zahodne et al., 2013) may be more effective future alternatives. In addition, although the relationship between CR and BRC are not yet well understood, early evidence suggests CR indices may be related to differences in underlying structural brain differences such as greater brain volume or synaptic density (Foubert-Samier et al., 2012). For example, additive (i.e., BRC + CR) or interactive (i.e., BRC x CR) effects may account for the individual differences in age-related changes in brain response patterns.

A better understanding of factors that influence neurocompensatory processes may aide healthy OAs in maintaining cognitive function, or *aging gracefully*. For example, sociological and cultural factors such as education, occupational complexity, social activity and physical exercise have been linked to maintenance of cognitive function in aging (Valenzuela et al., 2008; Katzman, 1993; Stern, 2012). Identification of functional brain changes associated with variables such as CR is a topic of growing interest (Barulli & Stern, 2013; Stern, 2016). Future research of age-related neurocompensatory processes may also aide researchers and clinicians in identifying problem areas in OAs (e.g., less efficient processing, overactivations associated with performance declines), and those at-risk of developing neurodegenerative conditions. Early identification of at-risk OAs may, in turn, inform intervention programs. A growing body of neuroimaging studies indicate that cognitive and physical exercise interventions induce structural

and functional changes associated with improved performance (for review, see Bamidis et al., 2014). Collectively, cognitive and physical training programs appear to be a promising alternative to pharmacological interventions for OAs and warrants future research.

CHAPTER 5

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APPENDIX A

TABLE 1

Demographic and Mean Summary Data

Variable	Mean	SD	Min	Max
Age (years)	63.78	7.99	53	83
Education (years)	16.36	1.96	12	21
WTAR (SS)	111.53	6.4	96	119
Nback	82.98	9.7	64	99

Notes: SS = standard score. 2-Back % includes correct hits and rejections proportional to the number of trials.
Education = years of formal education attained.

TABLE 2

Clusters of Significant Activation Response to the 2-Back Relative to Resting State using a Whole Brain Voxel-wise General Linear Model

Region	Voxels	x	y	z
L inferior/superior parietal lobule	300	33	52	41
R cerebellum	295	-24	55	-20
L cerebellum	87	31	54	-25
L precentral/postcentral gyrus	84	33	18	53
L inferior frontal/precentral gyrus	59	42	-4	33
R inferior parietal lobule	59	-42	43	40
L insula	47	29	-22	8
R superior parietal lobule	47	-29	62	42
R medial frontal gyrus	42	-8	-16	44
R insula	39	-32	-23	6
L medial frontal gyrus	34	7	-13	46
R middle frontal gyrus	31	-38	-28	29
L medial frontal gyrus	31	5	0	55
L middle frontal gyrus	18	40	-24	30

Notes: L = Left; R = Right; B = Bilateral. Coordinates reported in center of mass Talairach coordinates, RAI orientation. These clusters are shown in red in Figure 4.

TABLE 3

Clusters of Significant Deactivation Response to the 2-Back Relative to Resting State using a Whole Brain Voxel-wise General Linear Model

Region	Voxels	x	y	z
B medial frontal gyrus/anterior cingulate	771	1	-46	14
B posterior cingulate	322	2	48	27
L middle temporal gyrus	47	53	5	-11
R superior frontal gyrus	43	-16	-42	45
R postcentral gyrus	35	-20	42	64
L superior temporal gyrus	34	43	-17	-24
R middle temporal gyrus	32	-52	-2	-16
L middle temporal gyrus	25	48	67	25
R parahippocampal gyrus	19	-26	9	-14

Notes: L = Left; R = Right; B = Bilateral. Coordinates reported in center of mass Talairach coordinates, RAI orientation. These clusters are shown in blue in Figure 4. Axial view: z-plane coordinates: -25, -15, 2, 11, 35, 47, 60.

TABLE 4

Clusters of Significant Activation Response to the 2-Back Relative to the 0-Back using Whole Brain Voxel-wise General Linear Tests

Region	Voxels	x	y	z
L inferior parietal lobule	206	34	54	40
R inferior parietal lobule	171	-37	53	40
B medial frontal gyrus	109	0	-17	45
L middle/inferior frontal gyrus	108	42	-14	31
R middle frontal gyrus	85	-28	-7	50
R middle frontal gyrus	60	-41	-28	31
L middle frontal gyrus	52	27	-3	52
L insula	40	28	-23	6
L middle/superior frontal gyrus	32	31	-49	16
L cerebellum	27	30	57	-27
R cerebellum	27	-30	57	-26
R insula	24	-31	-24	5
R middle/superior frontal gyrus	21	-33	-52	17

Notes: L = Left; R = Right; B = Bilateral. Coordinates reported in center of mass Talairach coordinates, RAI orientation. These clusters are shown in red in Figure 5.

TABLE 5

Clusters of Significant Deactivation Response to the 2-Back Relative to the 0-Back using Whole Brain Voxel-wise General Linear Tests

Region	Voxels	x	y	z
B anterior cingulate/medial frontal gyrus	614	1	-39	2
L middle/superior temporal gyrus	176	50	-6	-17
B posterior cingulate	163	3	50	23
R superior temporal gyrus	41	-44	-19	-24
R insula/postcentral gyrus	28	-49	23	19
R precentral gyrus/insula	22	-50	3	9
R inferior parietal lobule	18	-5	28	27
L inferior frontal gyrus	16	19	-19	-7
L superior temporal gyrus	14	53	21	14

Notes: L = Left; R = Right; B = Bilateral. Coordinates reported in center of mass Talairach coordinates, RAI orientation. 2-Back deactivation response relative to the 0-Back reflects 0-Back > 2-Back effects. These clusters are shown in blue in Figure 5.

TABLE 6

Mean Intensity of Activation and Deactivation Effects of 2-Back versus Rest by Quadrant, Laterality Indices, and Posterior/Anterior Ratios

Mean Intensity Effects

Activation	Mean	SD	LI	P/A
Left Frontal	0.54	0.39	0.11*	0.04
Right Frontal	0.45	0.32		
Left Posterior	0.66	0.49		
Right Posterior	0.5	0.4		
Deactivation				
Left Frontal	-0.39	0.26	0.11*	-0.04
Right Frontal	-0.31	0.22		
Left Posterior	-0.4	0.36		
Right Posterior	-0.31	0.3		

Notes: * denotes left-lateralization of LI (Yuan et al., 2006)

TABLE 7

Mean Intensity of Activation and Deactivation Effects of 2-Back versus 0-Back by Quadrant, Laterality Indices, and Posterior/Anterior Ratios

Mean Intensity Effects

Activation	Mean	SD	LI	P/A
Left Frontal	0.54	0.36	0.05	-0.18
Right Frontal	0.52	0.4		
Left Posterior	0.42	0.34		
Right Posterior	0.37	0.31		
Deactivation				
Left Frontal	-0.18	0.18	0.23*	-0.11
Right Frontal	-0.11	0.12		
Left Posterior	-0.14	0.15		
Right Posterior	-0.12	0.14		

Notes: * denotes left-lateralization of LI (Yuan et al., 2006)

TABLE 8

Correlations among Study Variables: 2-Back Effects versus Rest

Activations

Variable	Age	Education	n-Back	LI	P/A
Age	-	-0.03	-0.18	.31*	-0.18
Education		-	0.05	0.07	0.13
n-Back			-	-0.12	0.16
LI				-	-0.05
P/A					-

Deactivations

Variable	Age	Education	n-Back	LI	P/A
Age	-	-0.03	-0.18	-.30*	0.17
Education		-	0.05	0.14	-0.04
n-Back			-	.36*	-0.02
LI				-	0.05
P/A					-

Notes: *p < .05

TABLE 9

Correlations among Study Variables: 2-Back versus 0-Back Effects

Activations

Variable	Age	Education	n-Back	LI	P/A
Age	-	-0.03	-0.18	0.06	-0.03
Education		-	0.05	-0.08	0.05
n-Back			-	0.35*	0.18
LI				-	0.05
P/A					-

Deactivations

Variable	Age	Education	n-Back	LI	P/A
Age	-	-0.03	-0.18	-0.19	0.2
Education		-	0.05	0.12	-0.2
n-Back			-	0.25	0.03
LI				-	0.04
P/A					-

Notes: *$p < .05$

TABLE 10

Multiple Regression and Moderation (CR) Analyses Predicting P/A: 2-Back Effects versus Rest

Activations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	-0.01	0.01		
	Education	0.02	0.02	0.05	0.05
2	Age	-0.01	0.01		
	Education	0.02	0.02		
	Age x Educ	0.00	0.00	0.08	0.03

Deactivations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	0.01	0.01		
	Education	0	0.02	0.03	0.03
2	Age	0.01	0.01		
	Education	-0.01	0.02		
	Age x Educ	0.00	0.00	0.05	0.02

Notes: CR = cognitive reserve; P/A = posterior/anterior ratio

TABLE 11

Multiple Regression and Moderation (CR) Analyses Predicting P/A: 2 Back versus 0-Back Effects

Activations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	0.00	0.00		
	Education	0.01	0.02	0.00	0.00
2	Age	0.00	0.01		
	Education	0.01	0.03		
	Age x Educ	0.00	0.00	0.01	0.01

Deactivations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	0.01	0.01		
	Education	-0.04	0.03	0.08	0.08
2	Age	0.01	0.01		
	Education	-0.04	0.03		
	Age x Educ	0.01	0.00	0.13	0.05

Notes: CR = cognitive reserve; P/A = posterior/anterior ratio

TABLE 12

Multiple Regression and Moderation (CR) Analyses Predicting LI: 2-Back Effects versus Rest

Activations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	0.01*	0.00		
	Education	0.01	0.02	0.10	0.10
2	Age	0.01*	0.00		
	Education	0.01	0.02		
	Age x Educ	0.00	0.00	0.11	0.01

Deactivations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	-0.01*	0.00		
	Education	0.01	0.02	0.10	0.10
2	Age	-0.01	0.00		
	Education	0.01	0.02		
	Age x Educ	0.00	0.00	0.11	0.00

Notes: * $p < .05$; CR = cognitive reserve; LI = laterality indices

TABLE 13

Multiple Regression and Moderation (CR) Analyses Predicting LI: 2-Back versus 0-Back Effects

Activations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	0.00	0.01		
	Education	-0.01	0.02	0.01	0.01
2	Age	0.00	0.00		
	Education	-0.01	0.02		
	Age x Educ	0.00	0.00	0.02	0.01

Deactivations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	-0.01	0.00		
	Education	0.01	0.02	0.05	0.05
2	Age	-0.01	0.00		
	Education	0.01	0.02		
	Age x Educ	0.00	0.00	0.09	0.04

Notes: CR = cognitive reserve; LI = laterality indices

TABLE 14

Multiple Regression and Moderation (2-Back performance) Analyses Predicting LI: 2-Back versus Rest Effects

Activations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	0.01	0.00		
	n-Back	0.00	0.00	0.10	0.10
2	Age	0.01	0.00		
	n-Back	0.00	0.00		
	Age x n-Back	0.00	0.00	0.10	0.00

Deactivations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	-.01	0.00		
	n-Back	.01*	0.00	0.19*	0.19*
2	Age	-.01*	0.00		
	n-Back	.01*	0.00		
	Age x n-Back	-.01*	0.00	0.26*	0.08*

Notes: *p < .05; LI = laterality indices

TABLE 15

Multiple Regression and Moderation (2-Back performance) Analyses Predicting LI: 2-Back versus 0-Back Effects

Activations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	0.00	0.01		
	n-Back	0.01*	0.00	0.14*	0.14
2	Age	0.00	0.00		
	n-Back	0.01*	0.00		
	Age x n-Back	0.00	0.00	0.14	0.00

Deactivations

Model	Variable	B	SE_B	R^2	R^2 change
1	Age	-0.01	00.0		
	n-Back	0.01	00.0	0.08	0.08
2	Age	0.00	00.0		
	n-Back	0.00	00.0		
	Age x n-Back	0.00	00.0	0.08	0.00

Notes: *p < .05; LI = laterality indices

APPENDIX B

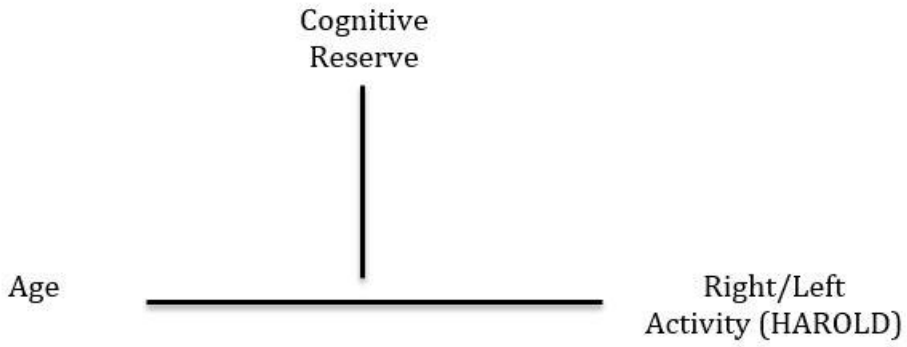

Figure 1. Proposed moderation model 1.

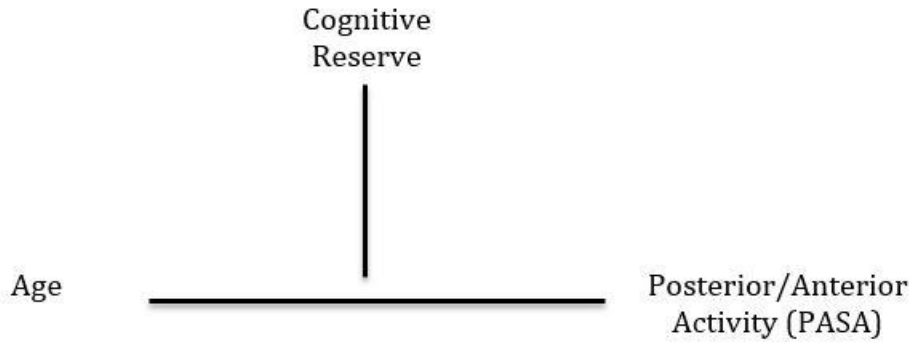

Figure 2. Proposed moderation model 2.

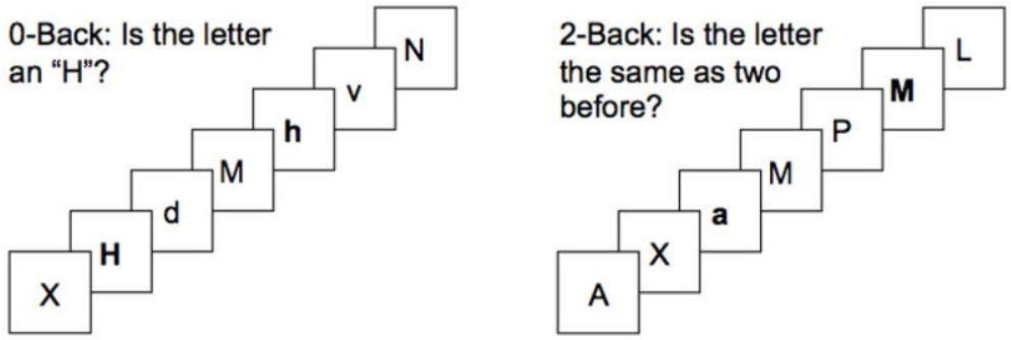

Figure 3. The n-Back paradigm

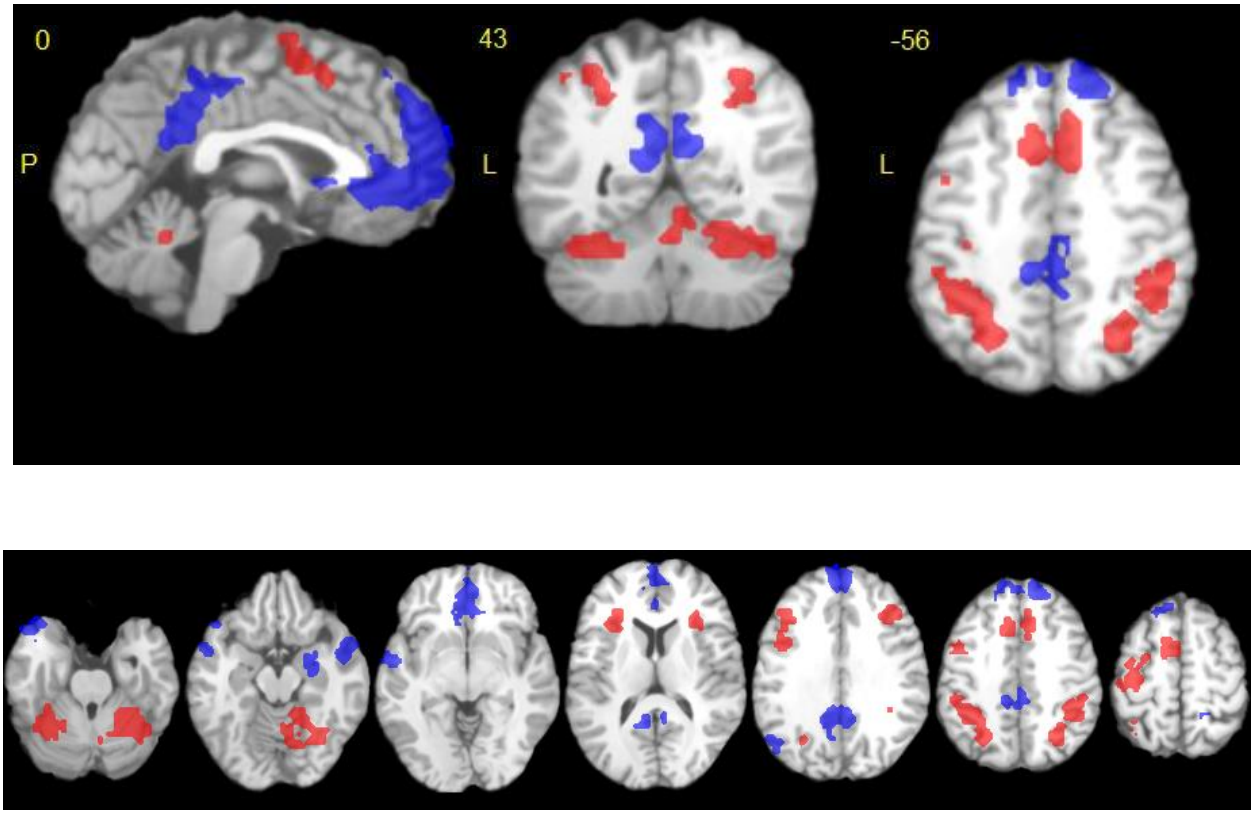

Figure 4. Clusters of significant brain response to the 2-Back relative to resting state using a whole brain voxel-wise general linear model.

Notes: P = posterior, L = left. Findings were thresholded at t-values of 9.0 (activations) and 7.9 (deactivations), respectively. Cluster centers of mass are reported in Tables 2 and 3. Axial view: z-plane coordinates: -25, -15, 2, 11, 35, 47, 60.

.

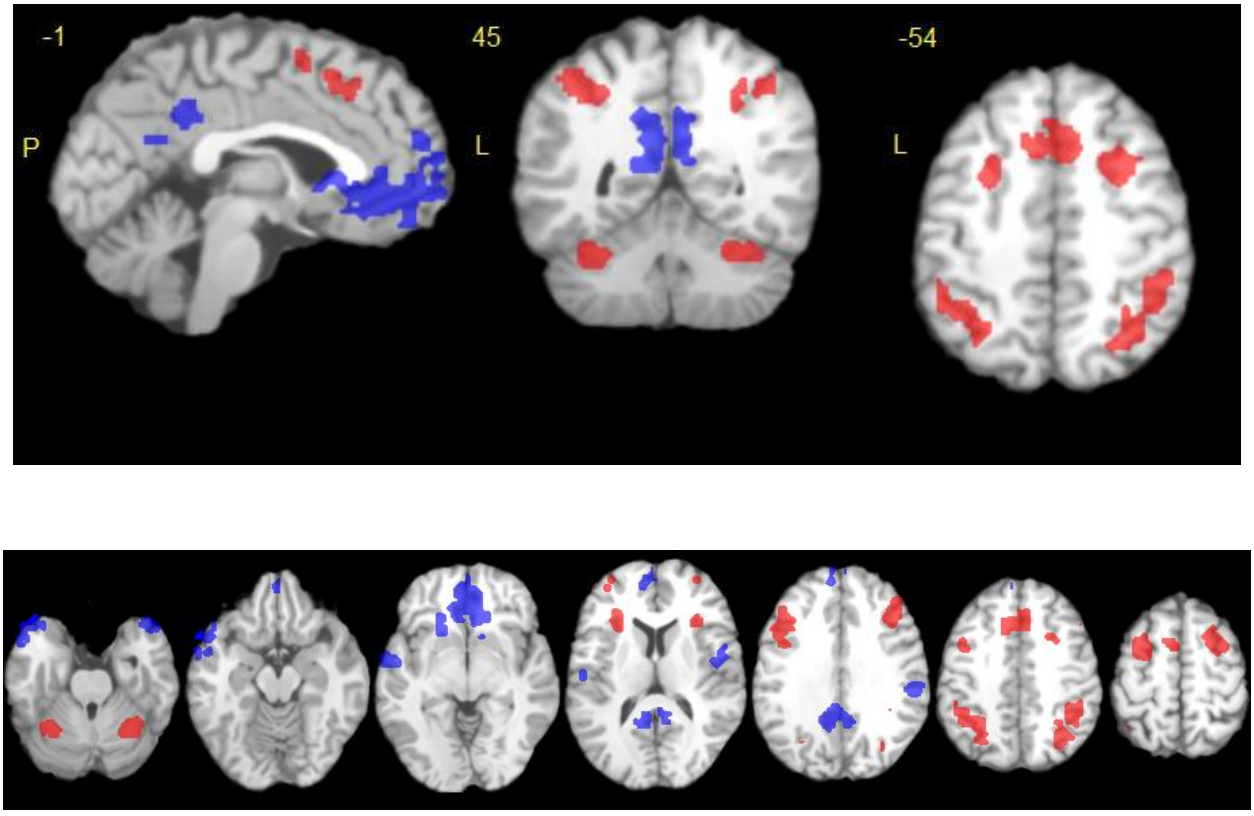

Figure 5. Clusters of significant brain response to the 2-Back relative to 0-Back using a whole brain voxel-wise general linear test

Notes: P = posterior, L = left. Findings were thresholded at t-values of 9.0 (activations) and 6.8 (deactivations), respectively. Cluster centers of mass are reported in Tables 4 and 5. Axial view: z-plane coordinates: -25, -15, -6, 11, 28, 41, 54.

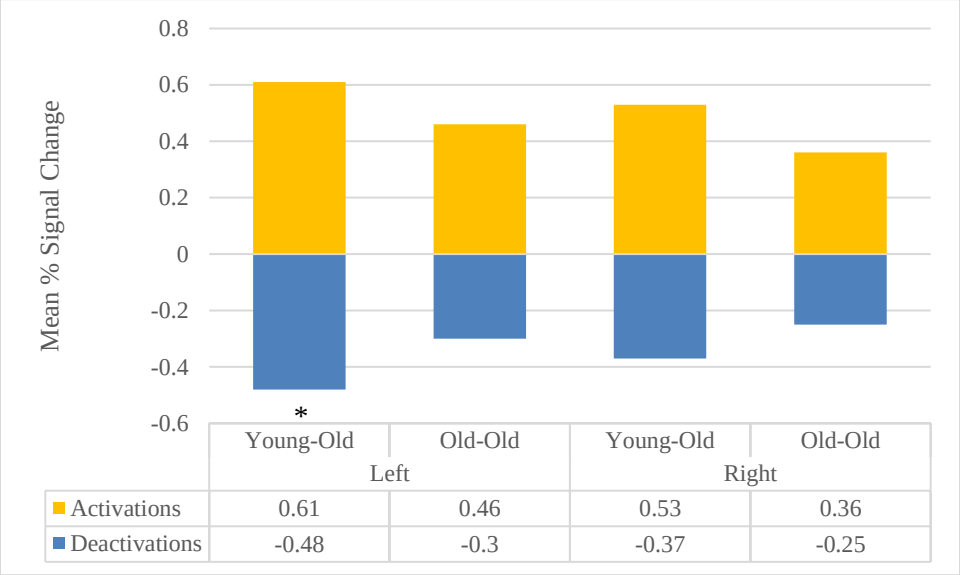

Figure 6. Mean effects of 2-Back versus resting baseline grouped to visualize components of the laterality indices as a function of age

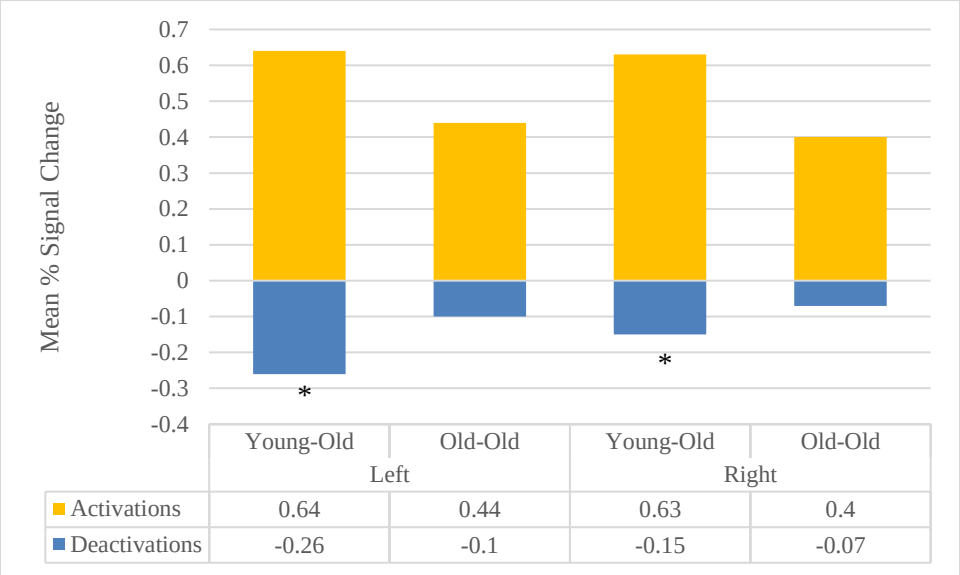

Figure 7: Mean effects of 2-Back versus 0-Back grouped to visualize components of the laterality indices as a function of age

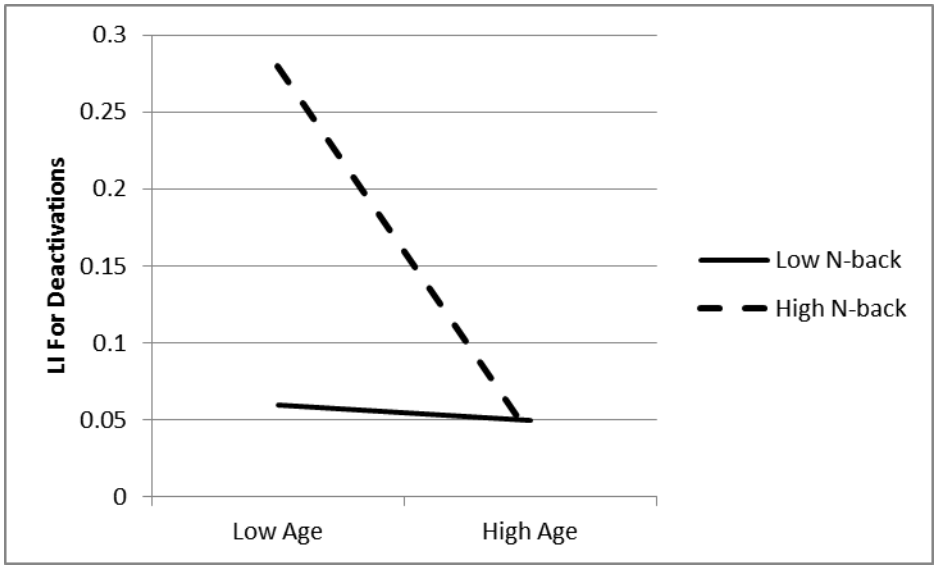

Figure 8: Simple slopes plot of conditional effects of n-Back

Notes: 2-Back performance moderates the relation between age and LI. Plot represents LI as predicted by age at fixed values of the moderator, n-Back: +1 standard deviation (9.7) and –1 standard deviation (-9.7) from the sample mean.