AGING AND CORTICAL RECRUITMENT IN RESPONSE TO COGNITIVE CHALLENGE

BY

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DISSERTATION

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ABSTRACT

Age-related changes in brain functional activation have been characterized by both age-related cortical over- and under-recruitment compared to young adults. Evidence from working memory domain has demonstrated that such neural responses reflect age-related differences in modulation of neural activity in response to increasing memory loads. The main focus of this thesis is to show that age-related cortical recruitment is modulated by task demands, constrained by individual's white matter integrity and external experience. In Experiment 1, I use the functional magnetic resonance imaging (fMRI) to reveal reduced BOLD-measured activity in older compared to young adults under demanding conditions in executive processing task, indicating clearly that the older adults have reduced or limited capacity of recruiting more neural resources in response to increasing task demands during cognitive control. In Experiment 2, I use the diffusion tensor imaging (DTI) to show that individual differences in micro-structural integrity of white matter, particular in corpus callosum, relate to both bilateral cortical recruitment and task performance in young and older adults, suggesting age-related degradation in white matter integrity of callosar fibers may be a contributing factor of reduced capacity to modulate neural resources in response to changing task demands in older adults. Finally, in Experiment 3, I additionally show the impact of cultural biases in contrast to fundamental biological effect in aging on bilateral cortical recruitment, suggesting that culture-related neural differences may remain at the same level throughout the lifespan. The series of studies jointly provide the evidence for age-related differences in modulation of cortical recruitment that may stem from structural changes in white matter integrity and culture-related differences in processing style.

ACKNOWLEDGEMENT

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CHAPTER 1

INTRODUCTION

There is a wealth of literature that documents age-related changes in fundamental cognitive processes across the lifespan (Park et al., 2002). Such universal age-related changes in cognition and behavior are characterized by both decline and preservation. Age-related declines were reported as a dominant picture of cognitive aging: the speed at which information is processed (Salthouse, 1996), sensory processing (Baltes & Lindenberger, 1997), the capacity of working memory (Park et al., 1996; 2002), the ability to selectively attend to relevant information (Hasher & Zacks, 1988), and the efficiency of sentence processing (Wlotko, Lee, & Federmeier, 2010) - all of these behavioral measurements of cognitive functions across several cross-sectional and longitudinal studies show age-related declines. In contrast, preserved cognition is evidenced by cross-sectional studies demonstrated that verbal knowledge and world knowledge (Park et al., 2002), and implicit, procedure memory (Howard et al., 2008) is relatively intact across the lifespan. Moreover, despite evidence showing memory deficit in older adults, the aspects of memory that rely more on familiarity-based processing than active recollection showed minimal impact with aging (for review see MacDaniel et al., 2008).

Functional neuroimaging of cognitive aging

However, these pictures of reliable decline with age in many behavioral and measurements of cognitive function looks quite different when neural function are further

examined by using neuroimaging tools such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Different patterns of age-related cortical *over-recruitment*, especially in the prefrontal cortex, have been frequently reported across several cognitive domains (Dennis & Cabeza, 2008; Fabiani, 2012; Grady, 2008; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008). These neural patterns are such that older adults appear to (1) exhibit increased activity in similar regions engaged by young adults, (2) reveal additional activation in regions that are not activated in young adults, and (3) elicit greater bilateral activity than the more unilateral activity observed in their young counterparts (Cabeza et al., 2002, 2004; Daselaar et al., 2003; Jimura & Braver, 2010; Morcom et al., 2003). These patterns could be due to either to compensatory mechanisms or to inefficiency of inhibitory processes. Moreover, age-related cortical *under-recruitment* in prefrontal cortex have also been identified, particularly under conditions of higher task demand such as executive processing tasks (de Chastelaine et al., 2011; Duverne et al. 2009; Grady et al., 1995; Logan et al., 2002; Nagel et al., 2009; Nielson et al., 2002; Langenecker & Nielson, 2003; Schneider-Garces et al., 2009; Cappell, Gmeindl, & Reuter-Lorenz, 2010) and may co-occur with the pattern of cortical over-recruitment (Colcombe et al. 2005; Langenecker, Nielson, & Rao, 2004; Milham et al., 2002).

A dominant observation of age-related over-recruitment is the bilateral activation of homologous prefrontal regions in older adults on tasks where their younger counterparts show unilateral activation pattern. Specifically, whereas young adults typically engage left lateralized frontal activity for tasks that involve verbal working memory, semantic processing, and recognition memory, older adults tend to show preserved left frontal

activity with additional contralateral recruitment in the homologous site of the right

hemisphere that is not observed in young adults (Cabeza et al., 1997; deChastelaine et al.,

2011; Daselaar et al., 2003; Davis et al., 2011; Duverne et al., 2009; Leshikar et al., 2010;

Madden et al., 1999; Reuter-Lorenz et al., 2000; Schneider-Garces et al., 2010). Similarly,

older adults engage both right and left prefrontal activity during tasks in which younger

adults engage only right lateralized prefrontal activity, such as in tasks associated with

face processing, spatial working memory, non-verbal spatial judgment, and episodic

recall (Cabeza et al., 1997; Grady et al., 1995; Park et al., 2010; Reuter-Lorenz et al.,

2000). This additional contralateral prefrontal recruitment that results in the pattern of

greater bilateral activation in older adults has been described as Hemispheric Asymmetry

Reduction in OLDer adults (HAROLD; Cabeza, 2002).

There is increasing evidence that the pattern of over-recruitment in older adults

appears to be compensatory and involved in the improvement or maintenance of

performance in the face of age-related neurodegeneration (Cabeza et al., 2004; Daselaar

et al., 2003; Davis et al., 2008; Grady, 2002; Gratton et al., 2009; Gutchess et al., 2005;

Heuninckx et al., 2008; Holtzer et al., 2009; Huang et al., 2012; Persson et al., 2004;

2006; Reuter-Lorenz et al., 2000; Rossi et al., 2004; Vallesi et al., 2011). For example,

Rossi et al. (2004) reported a direct evidence for the compensatory role of

over-recruitment in prefrontal regions in older adults by conducting a repetitive

Transcranial Magnetic Stimulation (rTMS), rTMS is a technique which transiently

disrupts neural function by applying repetitive magnetic stimulation to a specific area of

the brain, creating a temporally artificial brain lesion. Rossi et al. (2004) showed that

younger adults' memory retrieval accuracy was more affected when the rTMS was

applied to the left prefrontal cortex but less affected when rTMS was applied to the right prefrontal region. In contrast, older adults' retrieval accuracy was equally affected, whether rTMS was applied to the left or right prefrontal regions, suggesting bilateral prefrontal activation has a causal link to behavioral performance in older adults. A compensatory account of age-related over-recruitment was also supported in Morcom et al. (2003) who showed that greater frontal bilaterality in older adults compared to young predicted better performance when successfully encoding subsequently remembered items.

In addition to being beneficial for behavioral performance, evidence also suggests that increased neural effort observed in prefrontal cortex may reflect a compensatory response to deteriorating neural systems in more posterior sites of the brain, including the medial temporal lobe (Cabeza et al., 2004; Gutchess et al., 2005; Park et al., 2003), and occipital cortex (Cabeza et al., 2004; Davis et al., 2008; Goh et al., 2010). For example, Gutchess et al. (2005) showed that during an incidental memory encoding task, older adults had lower activation than young adults in the left and right parahippocampus and greater activation than young adults in the middle frontal cortex. Goh et al. (2010) also showed that increased frontal engagement was also associated lower neural selectivity in the ventral visual regions. Moreover, Cabeza et al. (2004) reported that older adults showed increased bilateral prefrontal activation and decreased occipital function compared to their young counterparts across various cognitive tasks, indicating a Posterior Anterior Shift in Aging (PASA) functional activity (Davis et al., 2008). These results suggest a neurocognitive compensatory role of prefrontal regions in older adults.

Alternatively, others have suggested that age-related cortical over-recruitment could

also be due to declined ability to efficiently select cortical processors appropriate for the task (i.e., non-selective recruitment) and reduced ability to efficiently inhibit inappropriate tissues for the task (Colcombe et al., 2005; Logon et al., 2002; Milham et al., 2002; Nielson et al., 2002), particularly under conditions of demanding executive/inhibitory control tasks. Along this line, Nielson et al. (2002) found that both young and older adults showed significant activation of right prefrontal regions during a go/no-go task, and older adults indeed showed additional recruitment in the left prefrontal cortex. However, in contrast to compensatory view reviewed previously, the additional activation exhibited by older adults was negatively correlated with individual's task performance. Similarly, Colcombe et al (2005) assessed individual differences in cortical recruitment using Flanker task in which young and older participants were asked to respond to a central arrow cue embedded in an array of arrows that pointed to either the left or the right. They reported that, despite older adults overall tended to show increased cortical recruitment compared to young adults, better performing older adults actually showed less bilateral activity pattern similar to the young. These results reflect an inability to efficiently select cortical processors appropriate for specific task requirement.

More recently, in addition to executive/inhibitory control data, some studies have reported impaired memory performance associated with additional contralateral prefrontal recruitment in older adults, suggesting that age-related cortical over-recruitment may not always be compensatory. For example, de Chastelaine et al. (2011) found that older adults' memory performance positively correlated with cortical over-recruitment in the left prefrontal cortex, a region also engaged by young adults. However, the correlation was negative with respect to additional recruitment in the right

prefrontal cortex of older adults, a region that was not observed in young adults, suggesting that over-recruitment in the right frontal regions in older individuals does not always contribute to their memory performance (see also Duverne et al., 2009).

The pattern of age-related cortical under-recruitment in prefrontal regions has also been reported with or without concurrent age-related cortical over-recruitment in some executive processing tasks. Such pattern is often interpreted to indicate that the older adults are functionally deficient in the processing operations mediated by this specific region (Langenecker et al., 2004; Milham et al., 2002), and may reflect the impairment due to poor strategies or reduced brain structure (Logan et al., 2002).

The Compensation-related Utilization of Neural Circuits Hypothesis (CRUNCH) has been proposed to accommodate these seemingly discrepant results in older adults (Reuter-Lorenz & Cappell, 2008). The CRUNCH hypothesizes that age-related *increases* in neural activity would occur with lower level of task demands where older adults would maintain relatively intact performance but that age-related *decreases* in neural activity would occur with higher levels of task demand where older adults' performance would suffer because at higher levels of task demand a resource ceiling is reached (Reuter-Lorenz & Lustig, 2005; Reuter-Lorenz & Cappell, 2008). In other words, there should be evidence for both over- and under-recruitment of neural resources, depending on the levels of task demand. This hypothesis further suggests that, compared to young adults, older adults have limited functional processing resources and reach their limitation of processing earlier, resulting in a less flexible modulation of neural activity in response to increasing task demands. By this view, the pattern of CRUNCH could also be observed on individuals with limited neural resources. Therefore, processing inefficiency would

cause the low performing individuals to recruit additional neural resources at low level of task demand to achieve computational output. As level of task demand become higher the high performing individuals would also need to engage additional neural resources to achieve the task goal, possibly resulting in more bilateral activity even in young individuals (Fabiani et al., 2012). Experiment 1 (Chapter 2) in thesis is thus designed to directly examine the CRUNCH idea and further address these age-related changes in modulation of neural activity in response to changing task demands during executive processing task.

Aging and the shrinkage of brain structure

Understanding the atrophy of aging brain is essential to the understanding of age-related changes in neural activity and cognitive performance. It has been suggested that age-related changes in neural activity occur as a response to age-related differences in brain structure (Park & Reuter-Lorenz, 2009). Therefore, age-related cortical recruitment may reflect "neural scaffolding" in response to gray matter shrinkage, white matter reduction, or amyloid deposition (e.g., Rodriguen et al., 2012)

There is wealth of evidence across several cross-sectional and longitudinal studies demonstrating that biological aging is characterized by reductions in gray matter volume (Raz et al., 2005; Resnick et al., 2003; Rodrigue & Raz, 2004), density (Good et al., 2001; Smith et al., 2007), and cortical thickness (Dickerson et al., 2009; Fjell et al., 2006, 2009; Salat et al., 2004), with the prefrontal, parietal and hippocampal regions showing greater shrinkage whereas the temporal and occipital regions showing minimal decrease. Moreover, there is also evidence that these age-related reductions in brain structure may

index specific cognitive decline in older adults. For example, age-related volumetric shrinkage in frontal gray matter have been related to lower fluid intelligence (Fjell et al., 2006; Head et al., 2008), and reduced hippocampal volume has been associated with poorer episodic memory (Head et al., 2008; Rodrigue & Raz, 2004).

In addition to the shrinkage in gray matter, biological aging is also associated with a reduction in white matter volume and density (Raz et al., 2005; Resnick et al., 2003; Salat et al., 2009; Walhovd et al., 2011). More recently, studies using diffusion tensor imaging (DTI), a non-invasive imaging technique, have suggested that white matter changes with aging highly involve a reduction in the integrity of white matter fibers that may be related to de-myelination along the axonal fibers and may result in less efficient conduction of neural signals and impaired transmission of information across the brain (for review, see Madden, Bennett, & Song, 2009; Sullivan & Pfefferbaum, 2006). The most consistent pattern of age-related difference in white matter fiber integrity is the greater reduction in the anterior regions of the corpus callosum, especially the genu and body of the corpus callosum and pericallosal frontal white matter, relative to the posterior regions of the corpus callosum (Davis et al., 2011; Gordon et al., 2008; Gunning-Dixon & Raz, 2003; Sullivan, & Pfefferbaum, 2006; Sullivan, Rohlfing, & Pfefferbaum, 2010). However, age-related declines in the posterior region of the corpus callosum (i.e. splenium) and the occipital white matter have been reported as well (Head et al., 2004; Kennedy & Raz, 2009a).

Inter-hemispheric interactions have been identified to play a key role during demanding tasks to prevent interference from the opposite hemisphere (Bonzano et al., 2008; Eliassen, Baynes, & Gazzaniga, 2000). The corpus callosum has been suggested to

connect homologous region between two hemispheres (Aboitiz et al., 1992; Hofer & Frahm, 2006), with the anterior and posterior portions of corpus callosum responsible for carrying a large proportion of white matter fibers connecting the two frontal and parietal cortices, respectively. Therefore, declines in corpus callosum size and microstructure with advancing age may result in age-related changes in behavioral performance. Moreover, it is possible to posit that such age-related changes in anterior and posterior portions of corpus callosum may be associated with an inability to modulate neural activity in response to changing task demands related to inter-hemispheric communication. Experiment 2 (Chapter 3) in thesis is thus designed to concurrently examine the relationship between age-related changes in white matter integrity, cortical recruitment, and behavioral performance during executive processing task.

In addition to biological aging, there is a compelling evidence indicating that a broad range of external experiences also affect both brain and behavior. Recent work in cognitive neuroscience has provided a wealth of evidence that sustained experience shapes cortical function and structures. For example, Wiesmann and Ishai (2010) recently reported that after short training session about Cubism, subjects exhibited better object recognition performance on Cubist paintings, with enhanced neural activation in the parahippocampal cortex. In a similar vein, London taxi drivers who engage in sustained wayfinding show larger gray matter of posterior hippocampal formation, with the magnitude of the effect increasing with experience, suggesting experiences to be the causal mechanism (Maguire et al., 2000). There is even evidence that sustained practice in learning to juggle increases the volume of cortical tissue in the bilateral mid-temporal area and left posterior intraparietal sulcus (Draganski et al., 2004), and that the effect was

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also observed when applying sustained practice to older adults (Boyke et al., 2008). With regard to experience and aging, one of the recent evidence for plasticity in neural function and structure in older adults were reported by Erickson et al. (2011), who found improved cognitive function and structural changes in hippocampal areas as a result of sustained aerobic exercise in older adults.

Cultural differences in cognitive and neural function

Given the evidence described above showing that external experiences sculpt the cognitive processes and neural organization, it is very reasonable to posit that sustained exposure to a set of culturally different experiences, value, viewpoints, and behavioral practices could also affect cognition, neural function and brain structure. A large literature of cultural psychology has provided innumerable demonstrations that there are subtle differences in the way individuals process information that appears to be a product of cultural experiences, with systematic differences observed between East Asians (e.g., Japan, Korea, and China) and Westerners (e.g., North America) with respect to visual perception, attention, and reasoning (Nisbett & Masuda, 2003; Nisbett, Peng, Choi, & Norenzayan, 2001) as well as motivation, relationality, and self-concept (Markus & Kitayama, 1991; Oyserman, Coon, & Kemmelmeier, 2002). Westerners, due to the individualistic, independent, and self-based focus of their culture, have a tendency to process focal objects and organize information via rules and categories in an analytic way. In contrast, East Asians, based on their collectivist and interdependent representation, tend to view themselves as part of a larger whole, resulting in a holistic information-processing bias where object and contextual information are jointly encoded

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(Goh & Park, 2009; Kitayama & Uskul, 2011; Masuda & Nisbett, 2001; Nisbett & Masuda, 2003; Park & Huang, 2010).

With regard to context-sensitive and object-oriented attention and memory, Japanese were more likely, after viewing an animated video clip of fish swimming in an underwater environment, to recall more information regarding contextual details and relationships between salient objects, whereas Americans referred more detail about the features of focal fish (Masuda & Nisbett, 2001). The cultural bias was observed on the perception of even simplistic and abstract visual stimuli. For instance, Kitayama, Duffy, Kawamura, and Larsen (2003) asked Japanese and Americans to reproduce the display after a framing square in which a vertical line was showed. Japanese tended to be more accurate at drawing the line in the relative (proportional) task suggesting better memory for contextual relationships, but Americans were more accurate in the absolute (context-dependent) task suggesting better memory for the exact size of the focal object. Other studies have focused on cultural differences on the incorporation of context into memory and reasoning. For example, Masuda and Nisbett (2001) presented East Asians and Westerners with target pictures against a complex background and reported that when backgrounds were replaced at recognition, East Asians were more sensitive to this disruption. There is also convincing evidence (Chiu, 1972; Ji, Zhang, & Nisbett, 2004) showing that, when making judgments about objects, Chinese children were more likely to process relationships among items more (e.g., cow-grass) whereas Westerners focus more on categories (e.g., cow-chicken), and evidence also exists that Westerners rely more on formal reasoning than intuition than East Asians (Norenzayan et al., 2002).

This cultural dichotomy presents a convenient lead into the exploration of how these

cognitive biases observed in behavior and cognition are manifested in the brain. A thorough review of neuroimaging studies associated with culture variables was presented by Han and Northoff (2008) and another review specifically of ventral visual cortex is presented by Goh and Park (2009). Here, we consider functional neuroimaging studies of cognition that focus on fronto-parietal networks. For example, using the Frame Line Test from Kitayama et al. (2003), Hedden et al. (2008) acquired fMRI data as Westerners and East Asians made absolute and relative line judgments in the scanner. They found that Westerners showed greater brain responses during relative compared to absolute line judgments in frontal and parietal regions, brain areas typically associated with attentional processing. In contrast, East Asians showed greater brain responses during absolute compared to relative judgments in the same regions. These findings suggest that participants required greater effort when engaging non-preferred visual processing styles, which is associated with cultural differences in attention-related responses in fronto-parietal regions. Importantly, the finding that Westerners required greater effort for relative judgments and East Asians for absolute judgments is again consistent with the analytic-holistic dichotomy in these two groups.

Cultural differences across age

A key question that arises when considering the influences of age and culture on cognitive and neural function is how they interact with each other over the human lifespan (Park & Gutchess, 2002; Park et al., 1999; Park & Gutchess, 2006). Three possible cases arise with respect to this interaction between age and culture. First, culture-related differences across individuals may accentuate with increasing age. With

increasing age, and assuming that individuals remain in the same cultural environment, individuals gain greater experience in their cultural environment. Such prolonged cultural exposure may result in more engrained psychological biases and also increasingly divergent expression of neural and cognitive development between different cultural groups. Second, culture-related differences, once attained, may remain at the same level throughout the lifespan. This case may arise because external cultural factors reach an asymptotic level of influence on neurocognitive processing, such that further experience does not increase the biases. Finally, culture-related neural differences may be reduced with increasing age. It is possible that age-related neurobiological changes impact all individuals to such a degree that differences in cognition and brain across older individuals is diminished relative to younger adults. Overall, these first two cases of age by culture interactions suggest that the neurobiological effects of age do not completely diminish individual differences in cognitive and neural function that arise from external experience. In contrast, the third case of an attenuation of culture-related differences with aging would suggest that the neurobiological effects of age exert a stronger influence on cognitive and neural function than cultural experiences.

Further, Chua et al. (2006) reported a cultural invariance of source memory across cultural groups when older and young Chinese and American participants were instructed to retrieve the source information previously presented by a video with statements by distinct speakers, along with pronounced age-related deficit in source memory observed in both cultures. The findings that there were equivalent age differences in source memory across cultural groups suggested that decreased ability on memory is likely represents a fundamentally neurobiological force of cognitive aging, rather than cultural

experience. In another study, Gutchess et al. (2006) examined categorical organization in a free recall task on 112 older and 112 young participants Chinese and Americans, using those categories that were normed to be equivalently familiar between two cultures. They found age-related deficit in free recall, with older adults recalling less items and performing worse in categorical clustering than young adults. Moreover, older Chinese showed less categorical clustering, whereas young Chinese used categorical clustering as much as young Americans in a highly related lists. The findings are consistent with the notion that sustained cultural exposure results in greater expression of cultural variation in information processing (Park & Gutchess, 2002; Park et al., 1999).

With respect to culture-related differences in older adults, Goh et al. (2007) used the fMRI adaptation paradigm to investigate ventral visual selectivity for objects and scenes in young and older, Westerners and East Asians. The main finding in that study was that older East Asians showed reduced object-related processing compared to the other three groups. This finding was interpreted as an accentuation of the bias for contextual processing in older East Asians due to a reduction in attentional resources with age. This result suggests that, despite aging causes an overall decline, biological aging may accentuate the cultural bias. In addition, distinct from the more global effect of aging on the brain, the effect of cultural experience on the brain appears to be more localized and specific. Experiment 3 (Chapter 4) in thesis is thus designed to investigate whether neural patterns of age-related changes in cortical recruitment are ubiquitous across individuals with different experiential background by conducting an across-cultural neuroimaging study in young and older adults.

In summary, this series of studies provide the missing links that demonstrate (1)

different patterns of age-related changes in cortical recruitment stem from a reduction in modulation of neural resources that limits older adult's ability to recruit more neural activity in response to changing task demand, (2) the source of the age-related changes in cortical recruitment may be traced to individual differences in white matter integrity of corpus callosum, and (3) these age-related differences in bilateral cortical recruitment may be selectively modulated by culture-related experiences. Three experiments were performed to arrive at these conclusions.

CHAPTER 2

THE EFFECT OF AGE ON UTILIZATION OF NEURAL CIRCUIT IN

RESPONSE TO CHANGING TASK DEMANDS

Introduction

Age-related changes in cortical recruitment have been characterized by both age-related cortical over- and under-recruitment compared to young adults. Specifically, the patterns of age-related cortical over-recruitment in prefrontal cortex have been frequently reported across several cognitive domains (Dennis & Cabeza, 2008; Park & Reuter-Lorenz, 2009), whereas the pattern of age-related cortical under-recruitment in prefrontal cortex has been identified particularly during task that place high demands on controlling processing. As reviewed earlier, models of age-related changes in brain function such as CRUNCH (Reuter-Lorenz & Cappell, 2008) was proposed to accommodate these seemingly discrepant neuroimaging results in older adults. The CRUNCH hypothesizes that there should be evidence for both over- and under-recruitment of neural resources in older adults, depending on the levels of task demand.

Thus far, some fMRI studies had directly examined the CRUNCH idea during working memory tasks and confirmed that age-related differences in prefrontal recruitment appear to depend on memory load. For example, in an initial work, Mattay et al. (2006) conducted a modified version of the "n" back working memory task at different levels of increasing working memory load (1-back, 2-back, and 3-back). They found that older adults performed equivalently with young adults and showed greater bilateral

prefrontal activity in 1-back condition (i.e., lower working memory load). At higher working memory load, however, older adults performed worse than young adults and showed relatively reduced prefrontal activity. These findings suggests that, compared to young adults, older adults have limited working memory capacity and reach their limitation of neural resources earlier, resulting in a decline in performance with increasing working memory demands. Holtzer et al. (2009) also reported a similar results using novel non-verbal material in working memory task. Yet, evidence linking age-related cortical recruitment in response to changing task demands to individual's capacity beyond their neural resources was unclear in these studies. According to CRUNCH, the curve relating cortical recruitment to processing load should not be linear but reach an asymptote at higher levels of task demand. Thus, it is necessary to parametrically manipulate at least four points of working memory load in a paradigm in order to examine this phenomenon.

Schneider-Garces et al. (2009) utilized a modified version of Sternberg memory task (Sternberg, 1966) with five levels of working memory set size (2-6 letters in the memory set). They demonstrated that, averaged across memory set size, older adults showed poorer performance and greater neural activation in fronto-parietal regions than young adults. In addition, however, when performed trend analyses separately at low (set size 2-4) and high (set size 4-6) levels of memory demand, young adults were able to increase prefrontal activity as the set size increased whereas older adults were engaging more prefrontal brain activity at lower set sizes that did not further increase, and even decreased, at higher set sizes. More interestingly, further analysis further demonstrated that once individual differences in performance (i.e., subjective levels of task demands)

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were accounted for, older and young adults showed similar patterns of brain activation. These findings provide a strong quantitative support for CRUNCH, with evidence for both age-related cortical over- and under-recruitment depending on memory load. Similar results were also reported when using verbal (Cappell et al., 2010) and spatial (Nagel et al., 2009) material in working memory paradigms. These converging findings suggested that, compared to young adults, older adults have a less flexible modulation of frontal activity in response to increasing working memory task demands.

It has been suggested that executive function such as working memory and cognitive control can be fractionated into dissociable cognitive and neural processes (Wager & Smith, 2003; Nee, Wager, & Jonides, 2007; Roberts & Hall, 2008). Cognitive control is associated with a network involving prefrontal and parietal association regions commonly active during task that place high demands on controlling processing (Badre & Wagner 2004; Duncan & Owen 2000; Miller & Cohen 2001). With regard to the effect of aging, many previous studies have reported both age-related increases and decreases in frontoparietal network during cognitive control tasks, including task switching (DiGirolamo, et al., 2001; Gratton et al., 2009; Jimura & Braver, 2010), control of response inhibition (Nielson et al., 2002, 2004; Vallesi et al., 2011; Zhu et al., 2010), motor control (Heuninckx et al., 2005, 2008) and interference resolution (Hedden et al., 2012; Huang et al., 2012; Langenecker et al., 2004; Milham, et al., 2002; Prakash, et al., 2009; Zysset et al., 2007). Age-related cortical over-recruitment in frontoparietal network was typically assumed to reflect greater engagement of top-down attentional processes and increased dependence on resolving conflict in older adults. In contrast, age-related decreased activity in the brain regions associated with cognitive control appeared to

reflect impairment in the implementation of cognitive control in older adults (Langenecker et al., 2004; Milham, et al., 2002; Prakash, et al., 2009). These findings in cognitive control domains are congruent with the CRUNCH notion that both age-related cortical over- and under-recruitment could be both reliable when task demands are varied. It thus raises the question of whether CRUNCH account of age-related functional brain changes can be generalized beyond working memory to cognitive control when the levels of task demand are systematically varied in one experiment.

Recent fMRI studies suggested a limitation in older adults' capacity to flexibly recruiting the specific brain region in response to increasing attentional control demands. For example, Prakash et al., (2009) conducted a modified version of color-word Stroop task and asked participants to respond to three ink colors of presented words: red, green, or purple. There was one congruent condition and two incongruent conditions (Incongruent-Eligible and Incongruent-Ineligible). In the congruent condition, the information conveyed by the word was consistent with the ink in which it was printed (e.g., the word RED printed in red ink); In the Incongruent-Eligible condition, the word matched one of the potential responses, but the ink-color was incongruent with the meaning of the word (e.g., the word GREEN printed in red ink), and in the Incongruent-Ineligible condition, the word did not match any of the potential responses, but the ink-color was incongruent with the meaning of the word (e.g. the word YELLOW printed in red ink). Greater attentional control is thus needed to perform the Incongruent-eligible condition compared to other conditions in this design. Prakash et al., (2009) found that young adults showed an increase in the activation of right middle frontal gyrus in response to increased levels of conflict (i.e., Incongruent-Eligible vs.

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Incongruent-Ineligible conditions), whereas older adults showed no increase in this specific region, indicating the less sensitivity and flexibility in response to increasing attentional control demands in right middle frontal gyrus (Prakash et al., 2009). However, they did not find any age-related difference within other regions, including left inferior frontal cortex, anterior cingulate cortex, or bilateral parietal cortices, which have been identified to require for overcoming the task-irrelevant information during attentional control.

The goal of this study is to directly examine the CRUNCH idea in the context of one of the cognitive control- interference resolution. Interference resolution is generally defined as cognitive control over dominant or automatic responses (Badre & Wagner 2004; Derrfusset al., 2005; Nee et al., 2007) and its neural correlates in young adults have been characterized in widespread fronto-parietal networks, including inferior and dorsolateral frontal regions, supplementary motor area (SMA), anterior cingulate cortex (ACC), posterior parietal cortices and cerebellum (Nee et al., 2007; Roberts & Hall, 2008). Regarding the effect of aging, some neuroimaging studies have shown age-related increases in the prefrontal and parietal activity during interference resolution, including task switching (DiGirolamo, et al., 2001; Gratton et al., 2009; Jimura & Braver, 2010), go/no-go paradigms (Nielson et al., 2002, 2004; Vallesi et al., 2011; Zhu et al., 2010), and Stroop-like paradigms (Huang et al., 2012; Mathis et al., 2009; Langenecker et al., 2004; Prakash, et al., 2009; Schulte et al., 2009; Zysset et al., 2007; Wood et al., 2009).

To investigate age-related changes in modulation of neural activity in response to changing task demands during cognitive control, we varied cognitive load for older and young adults using a modified version of the physical-numerical interference paradigm

(Besner and Coltheart, 1979; Kaufmann et al., 2005) across four levels of task demand. This Stroop-like paradigm includes two types of conflicts - physical size and numerical magnitude conflict – in two judgment tasks (Size task and Magnitude task) with identical stimuli but different types of response. Previous behavioral studies utilizing similar paradigm in young adults showed that performance was on average reduced in the Magnitude task compared to the Size task (Besner and Coltheart, 1979). In addition, recent fMRI studies demonstrated the greater as well as distributed frontoparietal activity for the Magnitude task than the Size task, suggesting an increased level of task demand for the Magnitude task (Huang et al., 2012; Kaufmann et al., 2005; Liu et al., 2006; Tang et al., 2006).

The data in the current experiment was initially analyzed in a prior study (Huang et al., 2012). Huang et al., (2012) investigated the functional significance of posterior parietal cortex when young and older performed the physical-numerical interference paradigm in MRI scanner. We found that, in the Incongruent vs. Congruent conditions contrast, young adults engaged more right parietal cortex for the Magnitude task and activated more left parietal cortex for the Size task, whereas older adults showed bilateral parietal activation for both Size and Magnitude tasks. These findings suggested a task-specific age-related neural recruitment in parietal cortex, as the hemisphere that was engaged depended on the judgment required. Moreover, we demonstrated the age-related additional parietal activity (i.e., right parietal for the Size and left parietal for the Magnitude task in older adults) was associated with better performance. Finally, as in many previous studies, we showed that older adults also recruited left prefrontal cortex during both tasks and this common activation was also associated with their better

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performance. These results provide evidence for task-specific compensatory recruitment in parietal cortex as well as task-independent compensatory recruitment in left prefrontal cortex during cognitive control in normal aging.

In addition, we re-analyzed the behavioral data in this prior work and found that behavioral results in reaction times suggest a successful manipulation of different levels of task demand in the physical-numerical interference paradigm. Specifically, behavioral results from a repeated measure ANOVA for reaction times data yielded a significant effect of age, of task, and of congruity: older adults were slower than young adults, responses on the Magnitude task were slower than the Size task, and the incongruent trials were slower than congruent trials. Moreover, there was also a reliable task x congruity interaction, with a larger congruity effect (incongruent vs. congruent trials) in the Magnitude task than in the Size task. The different levels of task demands across the Magnitude and the Size task thus provide a window to investigate age-related differences of neural activity in response to changing task demand during cognitive control. Therefore, the current experiment used this evidence in behavioral performance to guide the following fMRI analyses.

According to CRUNCH, processing inefficiencies cause the aging brain to recruit more neural resources to achieve computational output equivalent to that of the young brain, we thus predicted that (1) older adults would show reduced performance on average and greater neural activation across levels of task demand compared to young adults, (2) older adults would elicit greater frontoparietal activity in both low-conflict (i.e., congruent condition, larger in physical size is also larger in numerical magnitude) and high-conflict (i.e., incongruent condition, smaller in physical size is larger in numerical

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magnitude) conditions for the Size task, (3) older adults would show equivalent or reduced frontoparietal activity in high-conflict conditions for the Magnitude task due to the higher level of task demand, and (4) young adults would show more bilateral pattern of neural activation as level of task demand become higher because young individuals would also need to engage additional neural resources to achieve the task goal. These findings would suggest a reduced capacity for older adults to modulate neural resources in response to increasing task demand.

Methods

Participants

A total of 15 young adults (mean age = 25.5 years, ages 21-32 years; 9 females) and 18 healthy community-dwelling older adults (mean age = 66.1 years, ages 61-73 years; 9 females) participated in the study. The study was approved by the University of Illinois at Urbana-Champaign institutional review board and all participants gave informed consent prior to their participation. We discarded the data from 3 older participants because of excess motion (two participants) and image distortion due to improper headcoil placement (one participant).

All participants were right-handed native English speakers with normal or corrected-to-normal vision and had no prior history of psychiatric or neurological disorders. Young and older participants had a minimum score of 26 on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), with mean scores of 29.2 for young and 28.6 for old. Young and older participants had equivalent levels of

education and verbal ability as measured on the Shipley Vocabulary task (Shipley, 1986). In addition, older adults exhibited lower scores on the WAIS-R Digit-Symbol coding (Wechsler, 1997a), Pattern Matching and Dot Matching, which measured speed of processing, as well as Letter-Number Sequencing, and Forward and Backward Spatial Span (Wechsler Memory Scale- III, Wechsler, 1997b), which measured working memory. This pattern of stable crystallized ability (Shipley Vocabulary) with age and lower fluid abilities (speed and working memory) is typical of most cognitive aging samples in the literatures that focus on normal aging (Park et al., 2002). Group characteristics and results are reported in Table 1.

Experimental Materials and Design

Prior to entering the scanner, all participants underwent a short training session and practiced modified versions of the physical-numerical interference paradigm used by Besner and Coltheart (1979). Two types of judgment tasks were used in this modified paradigm to manipulate the levels of task demand: the Size task and the Magnitude task. In the Size task, participants were presented with a pair of digits and were asked to judge which digit was physically larger while ignoring the numerical magnitude of the digits. In the Magnitude task, participants were also presented with a pair of digits and were instructed to indicate which digit was numerically larger while ignoring their physical size. In both Size and Magnitude tasks, individual digits between 1 and 9, excluding 5 (Tzelgov, Meyer, & Henik, 1992), were used to create the digit pairs, and digit pairs were presented in Arial font with two different font sizes (55 and 73) to manipulate the physical size of the items.

For each task, two levels of conflict (i.e., low-conflict and high-conflict) were created by manipulating two types of conflicts, namely physical size and numerical magnitude conflict. In low-conflict condition (i.e., congruent trial), the digit that was larger in numerical magnitude was also larger in physical size, resulting in the reduced level of conflict between two types of conflicts. In high-conflict condition (i.e., incongruent trials), the digit that was larger in magnitude was smaller in physical size, resulting in the increased level of conflict between two types of conflicts. Neutral trials with regard to the task-relevant stimulus property were used as baseline conditions: for the Size task, neutral pairs involved the same numerical value (e.g., 6 6); for the

Magnitude task, neutral pairs had the same physical size (e.g., 2 6). Neutral trials containing the property of task in both the Size and the Magnitude tasks were not used because there was no manipulation of conflict. Combining the low-conflict and high-conflict conditions with the Size and the Magnitude tasks resulted in four levels of task demand: low-conflict Size, low-conflict Magnitude, high-conflict Size, and high-conflict Magnitude.

The functional MRI session was divided into four runs with two runs for each task. The order of the four runs was counter-balanced across participants, and stimuli within each run were presented randomly to control for order and fatigue effects. Each run consisted of 48 experimental trials, yielding 192 trials in total. The 48 trials within each run consisted of 16 low-conflict, 16 high-conflict and 16 neutral trials, with each trial consisting of a 500 ms fixation-cross and 500 ms blank screen followed by a 1000 ms presentation of the stimulus (Fig. 1). Trials were jittered and separated by inter-trial intervals (ITI) of 2, 4 or 6 s with a mean separation of 4 s (Dale, 1999). A resting period

of 21 s with a fixation-cross was presented at the beginning and end of each run, yielding a run lasting 330 s in total.

Stimuli were presented via E-prime (Psychology Software Tools, Pittsburgh, PA, USA) with a back-projection system. Participants viewed the stimuli using a mirror mounted on the headcoil and indicated their responses with a button press using the index and middle fingers of their right hand (Lumina response pad; Cedrus, San Pedro, CA, USA). Before each run, participants were orally and visually instructed to identify which digit in each pair was numerically (in the Magnitude task) or physically (in the Size task) larger, and to respond as quickly and accurately as possible.

Imaging Acquisition and Preprocessing

All fMRI sessions were conducted on a 3T MRI scanner (Allegra, Siemens, Germany) at the University of Illinois at Urbana-Champaign. For the experimental task, 165 functional scans were acquired in each run using a single-shot T2*-weighted gradient-echo Echo-Planar Image (EPI) sequence with TR/TE/FA= 2000 ms/60 ms/90°. Thirty-six contiguous axial slices were acquired with a slice thickness of 3 mm, 64 x 64 acquisition matrix, and 3.3 mm x 3.3 mm in-plane resolution. Co-planar structural T2 images were acquired to co-register the functional images to 3D-MPRAGE T1 structural image also acquired for each participant.

All preprocessing and General Linear Model (GLM) estimation was carried out using SPM2 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) implemented in MATLAB version 7.0 (The MathWorks, Natick, MA, USA). After discarding the first five volumes of each run, the functional images

were corrected for slice acquisition time and for participant motion, spatially normalized to the Montreal Neurological Institute (MNI) template and then spatially smoothed using an 8-mm full-width-at-half-maximum (FWHM) Gaussian kernel. Low frequency noise was also removed with a high-pass filter.

Data Analyses

Behavior

The accuracy and reaction times (RT) were analyzed with 2 x 2 x 2 mixed-design analysis of variances (ANOVAs) with age (Young adults, Older adults) as a between-subject factor and task (Size task, Magnitude task) and level of conflict (low-conflict, high-conflict) as within-subject factors.

fMRI: Whole Brain Analyses

The Size task and Magnitude task were modeled separately. Within each task, event-related BOLD responses for the low-conflict, high-conflict, and neutral conditions were modeled for each participant by convolving a vector of the onset times of the stimuli with the canonical hemodynamic response function (HRF) within the context of the GLM implemented in SPM2. Only correct trials were included in the models. For both the Size and Magnitude tasks, the resulting statistical parametric maps pertaining to each variable and effects of interest were calculated for each participant and then forwarded into a second-level analysis where each group served as a random-effects model. Significant regions of activation were identified using an uncorrected threshold of p<.001 and a minimum cluster size of 10 contiguous voxels.

fMRI: Regions-of-Interest Analyses

Signal change of functional activation. A region-of-interests (ROIs) approach was utilized to examine the effects of age and task demand for the strength of functional activation.

Two groups of ROIs were used in this fMRI analysis. The first group of ROIs was selected from the meta-analysis result in prior studies (Nee et al., 2007; Roberts & Hall, 2008), including left inferior frontal gyrus, right inferior frontal gyrus, left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, anterior cingulate cortex, left posterior parietal cortex, and right posterior parietal cortex. These brain regions have been proposed to be typically involved in the processing of cognitive control, namely "cognitive-control network". In addition, some researchers using Stroop-like paradigm to identify the neural correlates of cognitive control have suggested that these regions are sensitive to different levels of conflict and task demands (Mathis et al., 2009; Langenecker et al., 2004; Prakash, et al., 2009; Schulte et al., 2009; Zysset et al., 2007; Wood et al., 2009).

The second group of ROIs was selected from the results in a prior study (Huang et al., 2012). The brain regions that showed significant congruity effect (incongruent > congruent trials) for each task in the whole-brain analysis were used (see Table 3 in Huang et al., 2012). These regions include bilateral inferior frontal gyri, bilateral dorsolateral prefrontal cortex (including middle and superior frontal gyrus), anterior cingulate cortex, bilateral inferior parietal lobules, right supramarginal region, right superior parietal lobule, thalamus, and bilateral cerebellum (see Table 3 in Huang et al., 2012 for MNI coordinate of peaks).

To calculate averaged percent blood oxygenation level-dependent (BOLD) signal change, the voxel showing the largest t-value (i.e., local maxima) within our primary ROIs was then selected for each participant and for each level of task demand (i.e., low-conflict Size, low-conflict Magnitude, high-conflict Size, and high-conflict Magnitude). A spherical ROI with a 3-mm radius centered at local maxima of activated voxels was placed and an average percent BOLD signal change was calculated for this volume using Marsbar software (Brett et al. 2002).

Spatial extent of functional activation. Another ROIs analysis was designed to further investigate the difference in the spatial extent or spread of functional activations in the two groups.

To determine the spatial extent of functional activity within specific brain regions, two groups of ROIs used to measure the BOLD signal change of functional activation described above were selected: the first group of ROIs (i.e., cognitive-control network), includes left inferior frontal gyrus, right inferior frontal gyrus, left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, anterior cingulate cortex, left posterior parietal cortex, and right posterior parietal cortex. The second group of ROIs (reported in Huang et al., 2012) includes bilateral inferior frontal gyrus, bilateral dorsolateral prefrontal cortex (including middle and superior frontal gyrus), anterior cingulate cortex, bilateral inferior parietal lobules, right supramarginal region, right superior parietal lobule, thalamus, and bilateral cerebellum (see Table 3 in Huang et al., 2012 for MNI coordinate of peaks).

These ROIs were first identified in automated anatomical labeling (AAL, Tzourio-Mazoyer, et al., 2002) provided with SPM software to yield

anatomically-defined masks that used in the analysis. These masks of ROIs were then created and, following that, systematic assessments of the numbers of activated voxels were performed over these anatomically-defined masks on the statistical parametric maps pertaining to each variable and effects of interest that were calculated using an uncorrected threshold of p<.001 for each participant and for each level of task demand.

fMRI: Laterality Analyses

We next looked for evidence of age-related laterality differences in frontal, parietal, temporal and occipital cortices. The laterality was performed to systematically assess the laterality of activation over the brain regions that showed significant task-positive effects (i.e. low-conflict Size > Neutral condition, low-conflict Magnitude > Neutral condition, high-conflict Size > Neutral condition, and high-conflict Magnitude > Neutral condition) in the whole-brain analysis.

Laterality indices were based on the standard formula (Everts et al., 2009):

$$\text{Laterality} = [(\Sigma\text{voxel left} - \Sigma\text{voxel right})/(\Sigma\text{voxel left} + \Sigma\text{voxel right})]$$

This formula results in positive values for predominantly left-lateralized activity (laterality > 0.1), negative values for predominantly right-lateralized activity (laterality < -0.1), and values between 0.1 and -0.1 for bilateral activity (Everts et al., 2009; Powell et al., 2012).

To ensure the findings of age-related laterality differences in these regions were not due to the significance threshold selected for analyzing fMRI data (Cabeza, 2002), we computed laterality indices based on a variety of different activation thresholds and then computed a weighted average of the laterality indices, giving more weight to indices that

were computed using higher thresholds (Wilke & Schmithorst, 2006). This reliable approach has been utilized in several functions in neuroimging studies to assess the hemispheric asymmetry of verbal and visuospatial across the lifespan (Everts et al., 2009; Powell et al., 2012).

Results

Behavioral Results

The mean RT and accuracy data are presented in Table 2.

Accuracy

Results from a repeated measure ANOVA for accuracy revealed a main effect of task [$F(1,28) = 6.28$, $p < 0.05$], with lower accuracy for the Magnitude task compared to the Size task, and level of conflict [$F(1,28) = 41.10$, $p < 0.001$], with lower accuracy for the high-conflict condition compared to the low-conflict condition. The interaction between task and level of conflict was also significant [$F(1, 28) = 6.67$, $p < 0.005$] with a greater conflict effect (high vs. low) for the Magnitude task than the Size task. There was no significant effect of age on accuracy [$F(1,28) = 2.25$, $p = 0.15$], and age did not interact with task [$F(1,28) = 0.04$, $p = 0.84$] or level of conflict [$F(1, 28) = 0.64$, $p = 0.43$].

We were aware that both young and older adults appeared to show a ceiling effect of their performance in accuracy. The percent correct scores for the Size and the Magnitude tasks were then transformed into z scores based on distributions of groups (Reuter-Lorenz et al., 2000). Similar results from a repeated measure ANOVA for standardized accuracy were revealed: a main effect of task [$F(1,28) = 6.28$, $p < 0.05$], with lower accuracy for

the Magnitude task compared to the Size task, and level of conflict [F(1,28) = 41.10, p < 0.01], with lower accuracy for the high-conflict condition compared to the low-conflict condition. The interaction between task and level of conflict was also significant [F(1, 28) = 6.67, p< 0.05] with a greater conflict effect (high vs. low) for the Magnitude task than the Size task. There was no significant effect of age on standardized accuracy [F(1,28) = 2.08, p = 0.16], and age did not interact with task [F(1,28) = 0.57, p = 0.46] or level of conflict [F(1, 28) = 0.64, p = 0.43].

Reaction Times

Error trials were removed from all subsequent analyses of reaction time. The same age x task x level of conflict ANOVA on the RT data yielded a significant effect of age [F(1, 28) = 40.26, p< 0.01], of task [F(1, 28) = 32.37, p < 0.01] and of level of conflict [F(1, 28) = 169.69, p < 0.01]: older adults were slower, responses on the Magnitude task were slower, and the high-conflict condition was slower. There was also a reliable task x level of conflict interaction [F(1, 28) = 23.39, p < 0.01], with a larger conflict effect (high vs. low) in the Magnitude task than in the Size task. Once again, age did not significantly interact with task [F(1, 28) = 0.58, p = 0.45]. However, age x level of conflict interaction was marginal [F(1, 28) = 3.35, p = 0.078].

Summary

As predicted, older adults generally responded slower than young adults but with comparable accuracy. Both accuracy and RTs were worse on high-conflict condition compared with low-conflict condition and on the Magnitude task compared with the Size task. These behavioral results in RTs suggest a successful manipulation of different levels

of task demand and then we use this evidence to guide our following fMRI analyses.

fMRI Results: Whole Brain Analyses

To examine the age-related differences in modulation of neural activity in response to changing task demands, four levels of task demand were first analyzed separately for each age group. Fig. 2 shows the results (≥ 10 contiguous voxels with $p < 0.001$, uncorrected). The results showed different patterns of neural recruitment in response to changing task demand between two age groups. Young adults were likely to show pronounced increases in frontoparietal network with increasing task demands. In contrast, older adults appeared to show greater increases at the lower level of task demand (i.e., low-conflict Size condition and low-conflict Magnitude condition) but no further significant increases at the high level of task demand (i.e., high-conflict Size condition and high-conflict Magnitude condition).

A direct comparison between the two age groups demonstrates the age-related differences in modulation of neural activity in response to changing task demands (Fig. 2). Older adults showed greater and more distributed frontoparietal network in first three levels of task demands (i.e., low-conflict Size condition, low-conflict Magnitude condition, and high-conflict Size condition) compared to young adults (uncorrected threshold of $p<.001$). At the highest level of task demand (i.e., high-conflict Magnitude), however, older adults showed equivalent frontoparietal activity compared to young adults. In addition, we did not find any brain regions that exhibited greater activity in young adults compared to older adults in any level of task demand.

fMRI Results: ROI Analyses

Signal Changes of Functional Activation

To examine the strength of functional activation in response to changing task demand for young and older adults, activations in specific ROIs were measured as the average percent BOLD signal change (3-mm sphere surrounding the peak voxel) for four levels of task demand and for each participant.

The results from the first group of ROIs (i.e., cognitive-control network) showed that, despite the trend of increases in BOLD signal change as a functional of task demand were observed across the ROIs, two age groups appeared to elicit different patterns of neural recruitment (Fig. 3). Specifically, whereas the young adults showed reliably increased activity with increasing task demands, the older adults showed a pattern with a sharp increase at the lower level of conflict (i.e., low-conflict Size and low-conflict Magnitude) but a flattening at higher level of conflict (i.e., high-conflict Size and high-conflict Magnitude). In addition, such age-related patterns of neural recruitment in response to load effects appear to be more pronounced in right hemisphere compared to left hemisphere.

The t-tests between two age groups for each ROIs and for each level of task demand yielded several significant effects of age (Table 3). In low-conflict Size condition, older adults showed greater BOLD signal changes in left frontoparietal network; In low-conflict Magnitude and high-conflict Size conditions, older adults showed greater BOLD signal changes in bilateral frotoparietal network (but showed reversed and no effect in left posterior parietal cortex). In high-conflict Magnitude condition, however, older adults showed no significantly greater BOLD signal changes in frontoparietal

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network and showed even reduced signal changes in right inferior frontal gyrus.

The results from the second group of ROIs (i.e., ROIs reported in Huang et al. 2012) showed a similar pattern with the results of the first group ROIs (Fig. 4). Whereas the young adults showed reliably increased activity in front-parietal regions with increasing task demands, the older adults showed a pattern with a sharp increase at the lower level of conflict (i.e., low-conflict Size and low-conflict Magnitude) but a flattening at higher level of conflict (i.e., high-conflict Size and high-conflict Magnitude), particularly in bilateral inferior frontal gyri, bilateral dorsolateral prefrontal cortices, and anterior cingulate cortex.

The t-tests between two age groups for each ROIs and for each level of task demand yielded several significant effects of age (Table 4). Older adults showed significantly greater BOLD signal changes in most of prefrontal and parietal regions, thalamus, and cerebellum in lower levels of task demand (low-conflict Size, low-conflict Magnitude, and high-conflict Size conditions) but showed no significant increase in highest level of task demand (i.e., high-conflict Magnitude) except right superior parietal lobule and left cerebellum. These findings are consistent with the results using the cognitive-control network ROIs described above.

Spatial Extent of Functional Activation

To examine the spread of functional activation in response to changing task demand for young and older adults, activations in specific ROIs were measured as the spatial extent over the masks on each individual's statistical parametric maps (uncorrected threshold of p<.001) for each participant and each level of task demand. The

results are similar to the findings of signal-change approach presented above. The results from the first group of ROIs (i.e., cognitive-control network) showed that, although the trend of increases in spatial extent as a functional of task demand were observed across the ROIs, two age groups appear to show different patterns of neural recruitment (Fig. 5). Young adults showed reliably increased spatial extent with increasing task demands, whereas older adults showed a pattern with a sharp increase at the lower level of conflict but and a flattening at higher level of conflict. In addition, such age-related differences of neural recruitment in response to changing task demands appear to be pronounced in right hemisphere compared to left hemisphere.

The t-tests between two age groups for each ROI and for each level of task demand yielded several significant effects of age (Table 5). In low-conflict Size condition, older adults showed no greater spatial extent across ROIs; in low-conflict Magnitude condition, older adults showed greater spatial extent in bilateral inferior frontal gyri, right dorsolateral prefrontal cortex, and right posterior parietal cortex. Moreover, in high-conflict Size condition, older adults showed greater spatial extent in left inferior frontal gyrus and anterior cingulate cortex. In high-conflict Magnitude condition, however, older adults showed reduced spatial extent s in right dorsolateral prefrontal cortex and left posterior parietal cortex.

Similarly, the results from the second group of ROIs (i.e., ROIs reported in Huang et al. 2012) showed that two age groups appear to show different patterns of neural recruitment in spatial extent (Fig. 6). Specifically, in frontoparietal regions young adults showed the trend of increases in spatial extent with increasing task demands, whereas older adults showed a pattern with a sharp increase at the lower level of conflict but and a

flattening or a reduction at higher level of conflict. Similar age-related differences in spatial extents of functional activation were also observed in thalamus and bilateral cerebellar regions.

The t-tests between two age groups for each ROI and for each level of task demand yielded several significant effects of age (Table 6). In low-conflict Magnitude condition, older adults showed greater spatial extent in bilateral inferior frontal gyri, right dorsolateral prefrontal cortex, right inferior parietal lobule, and bilateral cerebellum. Moreover, in high-conflict Size condition, older adults showed greater spatial extent in left inferior frontal gyrus, anterior cingulate cortex, thalamus, and bilateral cerebellum. In high-conflict Magnitude condition, however, older adults showed no greater but reduced spatial extents of functional activation in right dorsolateral prefrontal cortex, left inferior parietal lobule, right superior parietal lobule, and right supramarginal region. These findings indicate that older adults have a reduced capacity to modulate neural resources in response to increasing task demands.

fMRI Results: Laterality Analyses

We next looked for evidence of the effect of task demand on laterality difference in young and older adults. According to CRUNCH, young adults would show greater bilateral pattern of neural activation with increasing task demands because young individuals would also need to recruit additional neural resources to achieve the computational output. The laterality index of activation over the brain regions that showed significant task-positive effects in individual's whole brain analysis was systematically assessed using boostraping approach (Wilke & Schmithorst, 2006). Figure

7 shows the results of laterality of frontal, parietal, temporal, and occipital regions for each group and each level of task demand.

The results demonstrated that in frontal cortex, older adults showed bilateral patterns of neural activation, whereas young adults revealed more right-lateralized activity across four levels of task demands. However, the two age groups showed different patterns of bilaterality with increasing task demand, with consistently bilateral activity for older adults but reduced right-laterality activity (i.e., greater bilateral activity) for young adults when task demands became higher. In addition, we did not find any age-related differences in laterality of neural activity for parietal, temporal, and occipital cortices.

Discussion

Our results provide evidence that while younger adults demonstrated an increase in the activation of cortical regions responsible for cognitive control when task demands become higher, older adults failed to modulate BOLD-measured activity within cognitive control network in response to higher levels of task demand. Such age-related differences in modulation of neural resources were identified in both the strength and the spread of functional activation. These findings suggest that older adults have reduced or limited capacities of recruiting more neural resources in response to increasing task demands. In addition, our findings are consistent with other previous works in working memory domain (Cappell et al., 2010; Holtzer et al., 2009; Mattay et al., 2006; Nagel et al., 2009, Schneider-Garces et al., 2009) and further constitute strong support for CRUNCH (Reuter-Lorenz & Cappell, 2008) in the context of cognitive control.

As described in Introduction section earlier, CRUNCH postulates that an additional

and/or bilateral recruitment of brain regions reflecting a compensatory activity would be progressively engaged with increasing task demands. We found that such pattern can also be observed in the form of bilateral recruitment across different levels of task demand even in young adults. Whereas older adults overall showed bilateral patterns of neural activation across task demands in frontal cortex, young adults revealed predominantly right-lateralized activation at the lower levels of task demand but showed increasing pattern of bilateral activation with increasing task demands (see Fig. 7). This phenomenon suggests that young adults may appear to manifest a compensatory activity when the executive processing task is sufficiently challenging. Along this line, Schneider-Garces et al. (2009) reported a typical pattern of age-related bilateral activation in young adults when subjective levels of cognitive effort (i.e., differences in working memory span across individuals) were taken into account. Moreover, similarly results were found in young low performing individuals with increasing task loads when both performance and age were considered in each group (young low performers, young high performers, old low performers, and old high performers) during spatial working memory task (Nagel et al., 2009). These findings suggest a continuum of additional/bilateral recruitment of neural resources across the lifespan, and moreover, age-related over-recruitment may not an emergence of new phenomenon (Fabiani et al., 2012; Hedden & Gabrieli, 2004). In other words, additional/bilateral cortical recruitment may be a process that characterized neural dynamics across the lifespan, and may reflect the normal reaction of neural circuits in response to cognitive challenge.

CRUNCH would predict significant age x task demands interaction in performance, with older adults showing intact performance at lower level of task demand and young

adults showing overall intact performance across task demands. Although marginally

significant [$F(1, 28) = 3.35$, $p = 0.078$], we note that congruent with the CRUNCH notion,

our behavioral results revealed a trend toward age x level of conflict on reaction times.

Specifically, older adults had disproportionate slower reaction times at higher level of

conflict conditions compared to young adults. These results suggest that increased

activity for young and older adults in a given condition may be a marker of compensatory

responses during cognitive control.

Universal age-related changes in behavior have been characterized by general

slowing in response times (Salthouse, 1996). Recently, some researchers have argued that,

due to the poor temporal resolution of fMRI technique, group differences in functional

brain activity may be confounded with group differences in their response times (Carp et

al., 2012). Therefore, despite similar hemodynamic effects for both young and older

adults, the accumulated blood flow over time (because of processing slowing) may result

in greater signal intensity for older adults. This could yield a potential confound to

interpret the phenomenon of age-related pattern of cortical recruitment. However, it is

unlikely that our findings of age-related difference in functional brain changes can be

attributed to the effect of response time, for two reasons. First, with regard to

within-group condition, older adults' reaction times were negatively correlated with their

signal intensity of activation in frontal as well as parietal regions (Huang et al., 2012).

Specifically, older adults showing faster reaction times were coupled with increased

BOLD signal intensity of left inferior frontal gyus across the Size and the Magnitude

tasks and with increased BOLD signal intensity in left and right posterior parietal cortices

for the Size and the Magnitude task, respectively. Second, with regard to between-group

condition, slower reaction times did not always cause increased BOLD signal intensity for young and older adults. In fact, older adults showing slower response times displayed decreased BOLD signal intensity in right inferior frontal gyrus than their young counterparts for high-conflict Magnitude condition (see Table 2, Fig 3 and Fig. 4). In addition, young adults showing faster reaction times displayed equivalent BOLD signal intensity in right inferior frontal gyrus for low-conflict Size condition (see Table 2 and Fig. 3). These findings indicate that, although BOLD-measured activity may be accumulated over time, the effect of reaction time appears to be unlikely the major cause of the age-related difference of functional brain activity in the present study.

Interestingly, we found that the increase of BOLD-measured activation showed a sigmoid rather than linear curve with increasing task demands, similar with the findings in previous study in working memory domain (Schneider-Garces et al., 2009). Such sigmoid pattern of BOLD-measured activation exhibited both a floor (left asymptote) effect and a ceiling (right asymptote) effect. Specifically, at very low level of task demand, the curve was flat (a floor). However, with increasing task demands, the curve rose steeply but become slightly flattened once individual's neural resources ceiling appeared to be reached (a ceiling). A critical question is what are the meanings of the presences of a floor and a ceiling for sigmoid pattern of BOLD-measured activation? Although it is difficult to make detailed inferences about physiological, psychological and/or neuronal contributions for the two effects, we offer a few speculations on this question.

Such sigmoid pattern of BOLD-measured activation could be possible due to age-related reduced capacity in neurovascular system (D'Esposito et al. 2003;

Kannurpatti et al. 2010). The reduced capacity of neurovascular system in older adults has been suggested to influence the BOLD signal of fMRI data. Such reduction in neurovascular capacity may result in the limitation of recruiting additional oxygenated blood of the aging brain, and further flushed out deoxyhemoglobin leading to the BOLD signal. Thus, older adults may reach their neurovascular ceiling at intermediate level of task demands. This would explain the results that an earlier asymptote occurs in the older (occurring about at high-conflict Size condition) than in the young adults (occurring beyond high-conflict Magnitude condition) in our fMRI data. Althought we cannot completely rule out the effect of age-related changes in neurovascular system on functional brain activation, we do note that our behavioral data clearly showed that the older adults' response times became much slower at about high-conflict Size condition, consistent with the observation in fMRI data, which may represent a real limit in processing capacity.

The ceiling effect could be associated with the upper level of limitation of individual's neural activity and cognitive ability. With regard to neuronal ceiling, the brain is not capable of providing further neuronal activity in a local circuitry at demanding task conditions. That is, no more neural resources are available. With regard to cognitive ceiling, it could be associated with the upper limit of individual's subjective capacity of cognitive load such as the inhibitory-control ability to filter out distracting task-irrelevant information (deletion), to prevent things from moving further into cognition (restraint), and access to working memory (access) (Hasher et al., 2008; Hasher & Zacks, 1988). Moreover, it would be possible that no more additional cognitive effort could be provided beyond this upper limit of individual's subjective capacity. By this

view, it is possible that the neural resources as well as cognitive ability could be increased when applying training, exercise, and other interventions (Park & Bischof, 2011). Conversely, sleep deprivation, neurological damages, and stress may reduce the capacity of neuronal and cognitive resources and lower the resource ceiling somehow (Chee et al., 2008; Reuter-Lorenz & Cappell, 2008).

In contrast, the floor effect could be just a neuronal noise or a threshold used for statistical analyses. It has been suggested that a floor effect of brain imaging data may reflect an artifact due to the insensitivity of the hemodynamic measures in fMRI for lower levels of neural activation (Fabiani, 2012; Schneider-Garces et al., 2009). Moreover, the existence of floor effect in the present study could be the reliable BOLD-measured activity that required minimum resources in order to maintain multiple representations of task-relevant information such as number and size without any conflict between these two representations. The relevant continuous quantities of numerical magnitude and physical size have been suggested to share the overlapping representation at semantic and perceptual levels in human (Besner & Coltheart, 1979; Henik & Tzelgov, 1982). At neural level, fMRI studies also reported that numerical magnitude and physical size appeared to be represented in distributed and overlapping neural resources, with number and size engaging a common parietal spatial code and size engaging more occipito-temporal perceptual representation (Pinel et al., 2004; Walsh 2003). Thus, given the property of paradigm in both the Size and the Magnitude tasks in the present study, the floor effect of brain activity exists may reflect the processing resources to preserve distinct representations between number and size. Following that, with increasing task demands (i.e., the manipulation of conflict) the brain activity indexed by the growing

portion of the nonlinear sigmoid curve is thus a reflection of the mutual interference/conflict between two representations. In addition, variations with changing task demands required to go beyond the floor level could reflect individual differences in processing capacity to keep distinct representation, and further, filter out the task-irrelevant information. With regard to the effect of age, such processing capacity could be reduced due to their less distinctive representations (Goh et al., 2010; Park et al., 2004) as well as inefficient inhibitory processes (e.g., Gazzaley et al., 2005, 2008).

An interesting observation from this experiment was that the reduced capacity of recruiting neural resources in response to increasing task demands in the aging brain appears to be greater for right hemisphere than for left hemisphere at demanding conditions, suggesting a hemispheric difference of the limitation in processing capacity with aging. This result raises the possibility that age-related reduction in integrity of callosal fibers may mediate the inter-hemispheric cortical recruitment in response to changing task demands (Gratton et al., 2009). Thus, an important subsequent question is whether age-related changes in cortical recruitment could be due in part to reduced integrity of the white matter structural connectivity in the brains of older adults.

Tables

Table 1. Participant characteristics, demographics, and neuropsychological assessment (Means and standard deviations).

	Young		Older		
	Mean	SD	Mean	SD	P value
Age	25.53	3.48	66.07	4.15	.00**
Year of education	16.67	1.99	16.47	2.03	.79
Mini-Mental State Exam	29.20	1.42	28.60	0.99	.19
Shipley Vocabulary Task	34.87	3.11	36.36	2.27	.16
Pattern Matching	43.13	5.63	30.20	7.85	.00**
Dot Matching	17.00	2.93	10.27	2.81	.00**
Letter-Number Sequencing	15.27	1.94	11.47	3.62	.00**
WAIS-R Digit-Symbol	79.47	8.76	58.53	9.43	.00**
WAIS-R Information	24.20	2.62	24.40	3.44	.86
WMS-III Forward Spatial Span	10.20	1.61	7.47	1.51	.00**
WMS-III Backward Spatial Span	9.53	1.60	8.27	1.44	.03*

* denotes p<.05, ** denotes p<.01

Table 2. Response times (ms), mean accuracy and standard deviations for young and older adults in the Size task and the Magnitude task with the level of conflict.

	Young		Older	
	RTs (ms)	Accuracy	RTs (ms)	Accuracy
	Size Task			
Low-conflict	449.6 (43.0)	0.99 (0.0)	550.5 (75.8)	0.99 (0.0)
High-conflict	506.7 (59.5)	0.95 (0.1)	642.1 (101.3)	0.97 (0.0)
	Magnitude Task			
Low-conflict	503.4 (54.6)	0.98 (0.0)	636.4 (84.2)	0.99 (0.0)
High-conflict	608.4 (76.5)	0.93 (0.1)	759.8 (83.7)	0.94 (0.1)

Note: Numbers in parentheses denote standard deviations.

Table 3. Group differences in BOLD signal changes of functional activation for each level of task demand and each ROI (ROIs from cognitive control network).

	Low-conflict		High-conflict	
	Size	Magnitude	Size	Magnitude
Left IFG	2.09**	2.78***	3.31***	-0.30
Right IFG	-0.21	1.40*	1.50*	-2.52***
Left DLPFC	1.41*	2.58***	3.87***	0.04
Right DLPFC	0.77	3.10***	3.16***	-0.73
ACC	0.40	1.37*	2.74***	0.06
Left PPC	2.94***	-2.36**	1.31	0.61
Right PPC	0.70	3.15***	2.40**	0.77

IFG, Inferior frontal gyrus; DLPFC, dorsolateral prefrontal cortex; ACC, Anterior Cingulate Cortex; PPC, posterior parietal cortex. *p < .1; **p < .05; ***p < .01.

Table 4. Group differences in BOLD signal changes of functional activation for each level of task demand and each ROI (ROIs from a prior study).

	Low-conflict		High-conflict	
	Size	Magnitude	Size	Magnitude
Left IFG	0.59	2.46**	5.36***	1.21
Right IFG	2.04**	2.53***	2.94***	-1.24
Left DLPFC	1.97**	4.69***	3.55***	1.29
Right DLPFC	2.83***	3.17***	4.10***	0.66
ACC	2.77***	1.29	1.62*	-0.81
Left IPL	2.94***	-0.13	1.31	1.02
Right IPL	2.70***	3.93***	1.83**	0.77
Right SPL	2.29**	3.13***	5.21***	1.70*
Right SPG	0.82	1.65*	3.53***	-0.49
Thalamus	2.57***	-0.41	2.99***	-0.33
Left Cerebellum	5.31***	2.58***	0.13	2.00**
Right Cerebellum	0.09	1.28	0.98	-0.16

IFG, Inferior frontal gyrus; DLPFC, dorsolateral prefrontal cortex; ACC, Anterior Cingulate Cortex; IPL: inferior parietal lobule; SPL: superior parietal lobule; SPG: supramarginal region. $*p < .1$; $**p < .05$; $***p < .01$.

Table 5. Group differences in spatial extent of functional activation for each level of task demand and each ROI (ROIs from cognitive control network).

	Low-conflict		High-conflict	
	Size	Magnitude	Size	Magnitude
Left IFG	-0.20	1.98**	2.06**	0.58
Right IFG	-0.97	1.36*	1.11	-0.21
Left DLPFC	-1.05	0.75	0.04	-1.25
Right DLPFC	-0.69	1.35*	1.27	-1.51*
ACC	-0.82	0.30	1.40*	-1.05
Left PPC	-1.14	0.78	1.07	-1.46*
Right PPC	-1.13	1.85**	0.29	-0.84

IFG, Inferior frontal gyrus; DLPFC, dorsolateral prefrontal cortex; ACC, Anterior Cingulate Cortex; PPC, posterior parietal cortex. *p < .1; **p < .05; ***p < .01.

Table 6. Group differences in spatial extent of functional activation for each level of task demand and each ROI (ROIs from a prior study).

	Low-conflict		High-conflict	
	Size	Magnitude	Size	Magnitude
Left IFG	-0.20	1.98**	2.06**	0.58
Right IFG	-0.97	1.36*	1.11	-0.21
Left DLPFC	-1.06	0.75	0.04	-1.25
Right DLPFC	-0.69	1.35*	1.27	-1.51**
ACC	-0.82	0.30	1.40*	-1.05
Left IPL	-1.14	0.78	1.07	-1.46*
Right IPL	-1.13	1.85**	0.29	-0.84
Right SPL	-1.28	0.71	0.37	-2.15**
Right SPG	-0.73	0.59	0.46	-1.88**
Thalamus	-0.39	0.60	2.20**	-0.64
Left Cerebellum	-0.36	1.50*	2.65***	-0.30
Right Cerebellum	0.28	1.47*	2.42**	0.23

IFG, Inferior frontal gyrus; DLPFC, dorsolateral prefrontal cortex; ACC, Anterior Cingulate Cortex; IPL: inferior parietal lobule; SPL: superior parietal lobule; SPG: supramarginal region. *p < .1; **p < .05; ***p < .01.
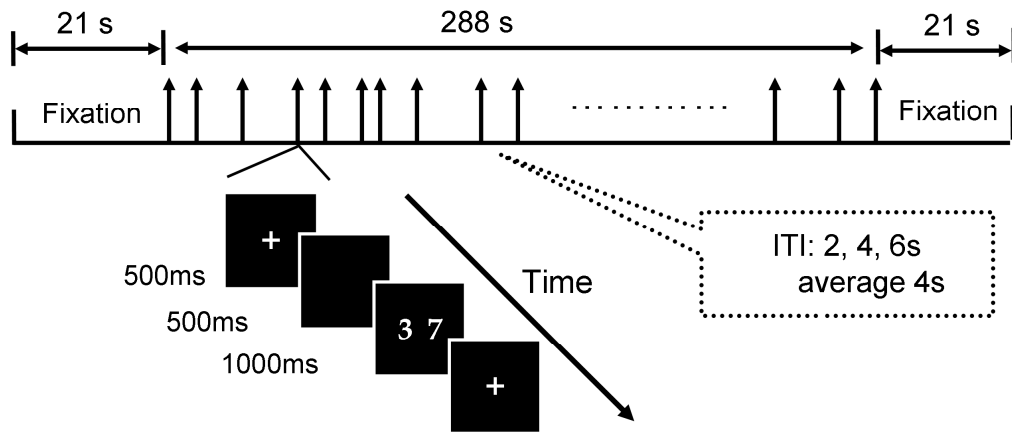
Figures

Figure 1. Experimental procedures showing sample stimuli for the low-conflict, neutral, and high-conflict conditions in both tasks. Each trial consisted of a 500 ms fixation-cross and 500 ms blank screen followed by a 1000 ms presentation of the stimulus. Inter-trial-intervals (ITI) varied between 2, 4, and 6 s. The physical size task and numerical magnitude task each occurred twice in counter-balanced order across participants.
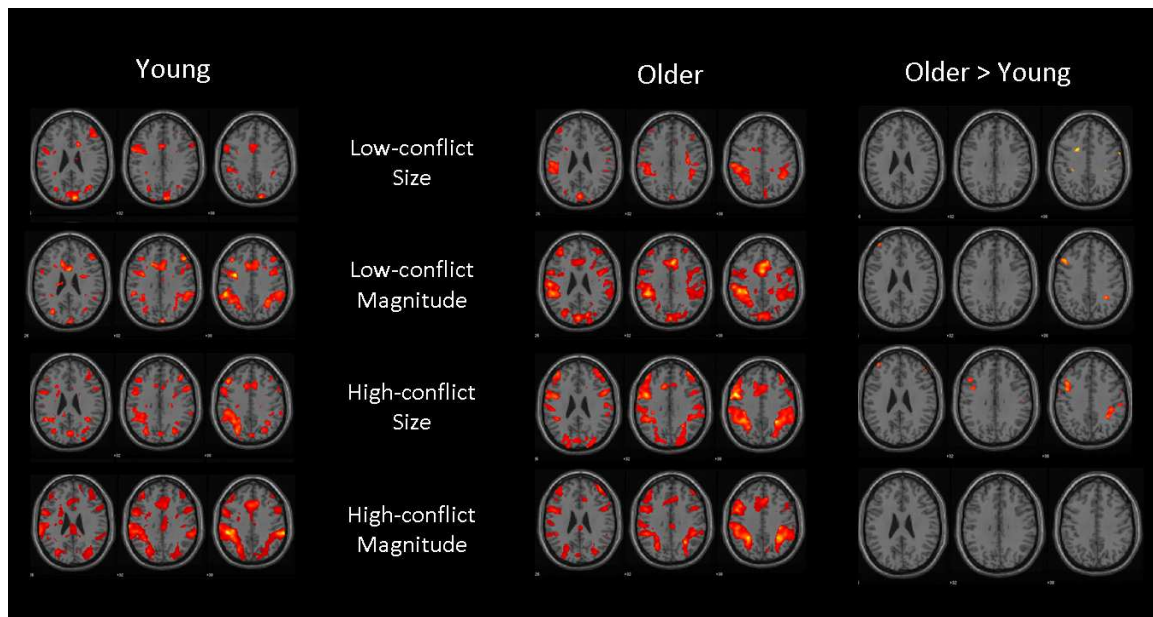
Figure 2. The statistical brain maps (axial view) of each level of task demand (low-conflict Size, low-conflict Magnitude, high-conflict Size, and high-conflict Magnitude) for young (left), older (middle) adults, and the effect of age (right) (≥10 contiguous voxels with p < 0.001, uncorrected).
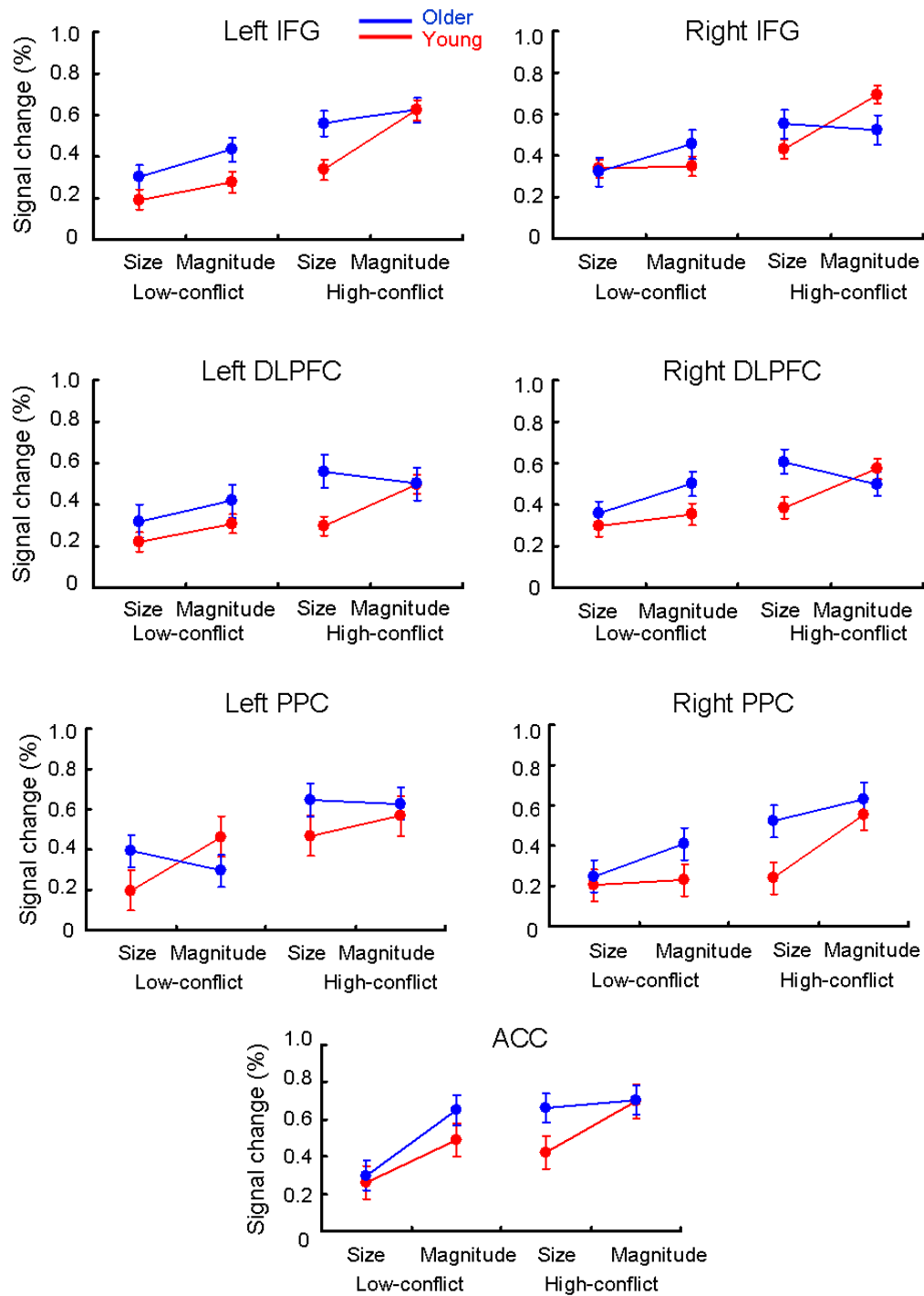
Figure 3. ROI analyses of the percent BOLD signal change in cognitive-control network. The ROIs include bilateral inferior frontal gyrus (IFG), bilateral dorsolateral prefrontal cortex (DLPFC), and bilateral posterior parietal cortex (PPC), and anterior cingulate cortex (ACC) for older (blue) and young (red) adults. Percent signal changes were calculated for each participant and each level of task demands (against fixation baseline).
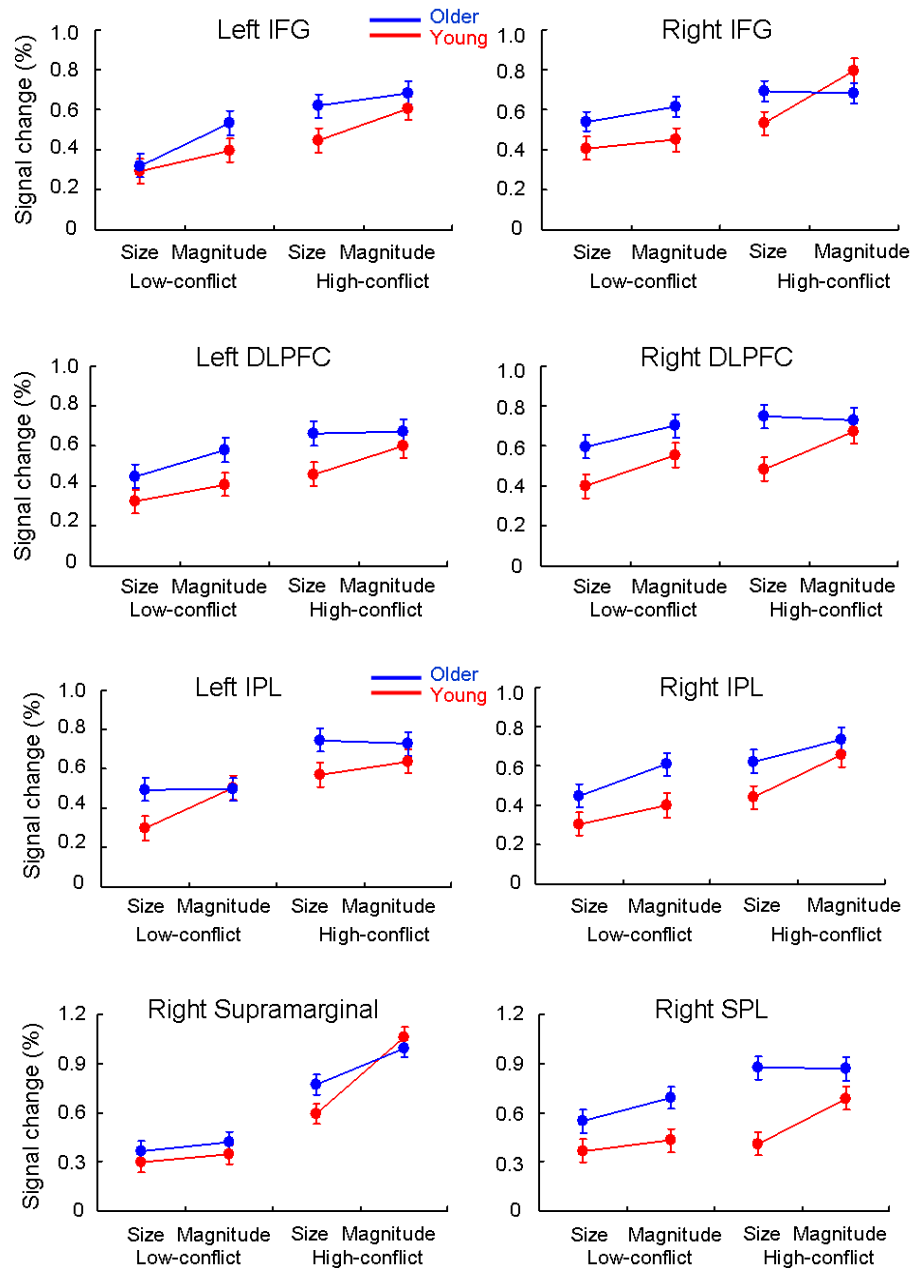
Figure 4. ROI analyses of the percent BOLD signal change. The ROIs were selected from a prior study (see Methods). The ROIs include bilateral inferior frontal gyrus (IFG), bilateral dorsolateral prefrontal cortex (DLPFC), and bilateral inferior parietal lobule (IPL), right supramarginal region, right superior parietal lobule (SPL), anterior cingulate cortex (ACC), thalamus, and bilateral cerebellum for older (blue) and young (red) adults. Percent signal changes were calculated for each participant and each level of task demands (against fixation baseline).
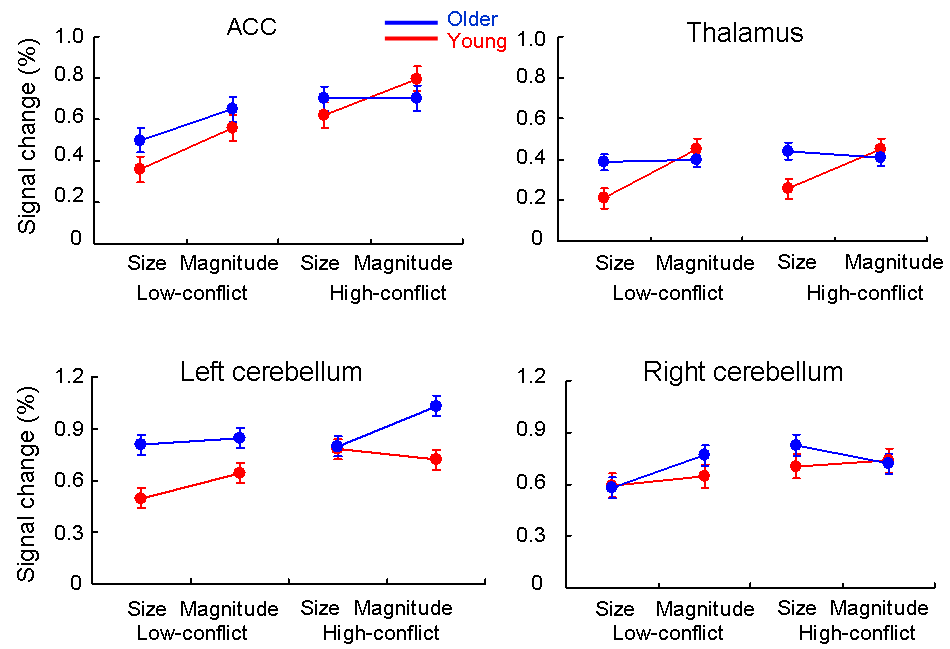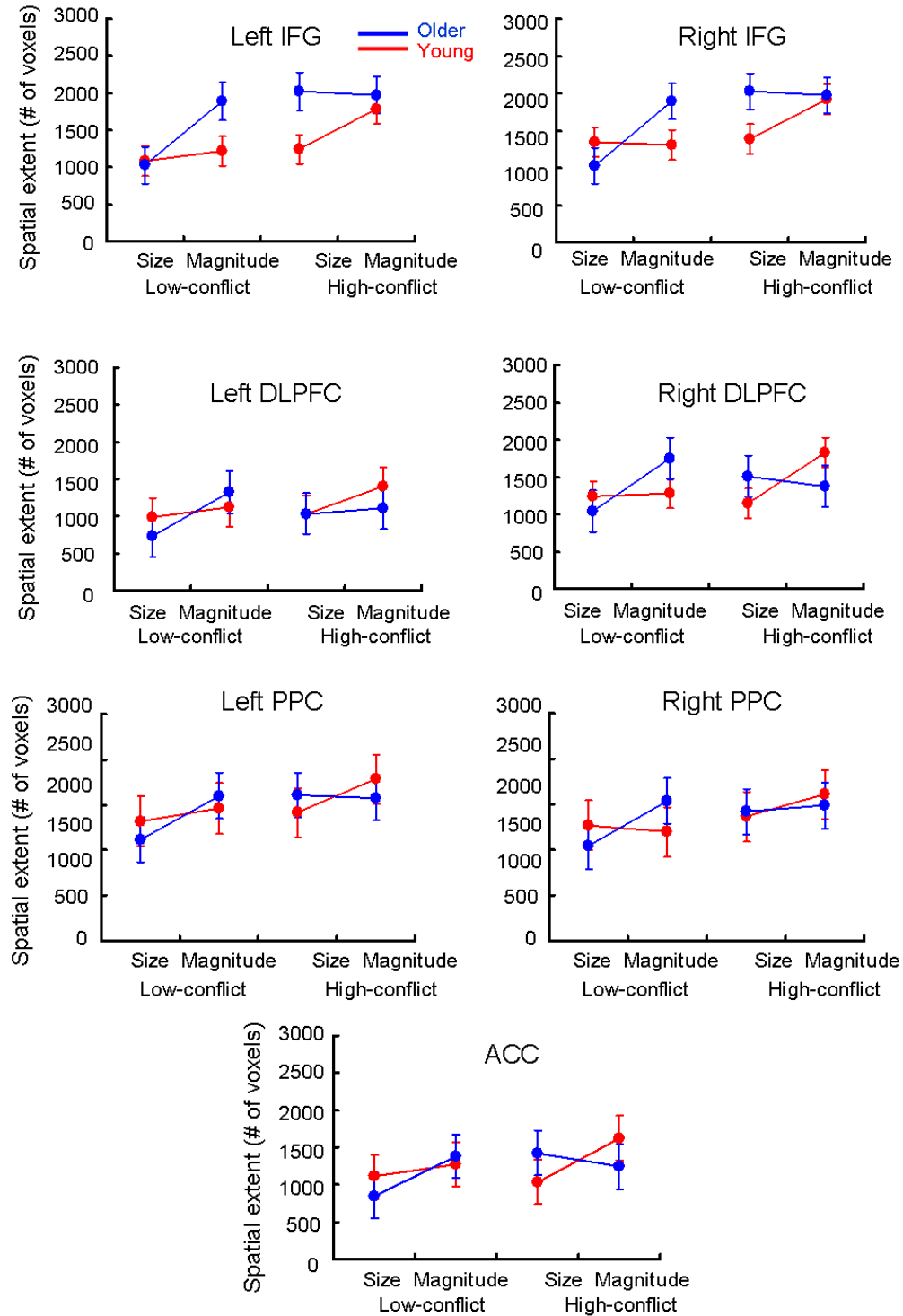
Figure 4 (cont.)

Figure 5. ROI analysis of the spatial extent in cognitive control network. The ROIs include bilateral inferior frontal gyrus (IFG), bilateral dorsolateral prefrontal cortex (DLPFC), bilateral posterior parietal cortex (PPC), and anterior cingulate cortex (ACC) for older (blue) and young (red) adults. Spatial extent was calculated using an uncorrected threshold of p<.001 for each participant and for each level of task demand.
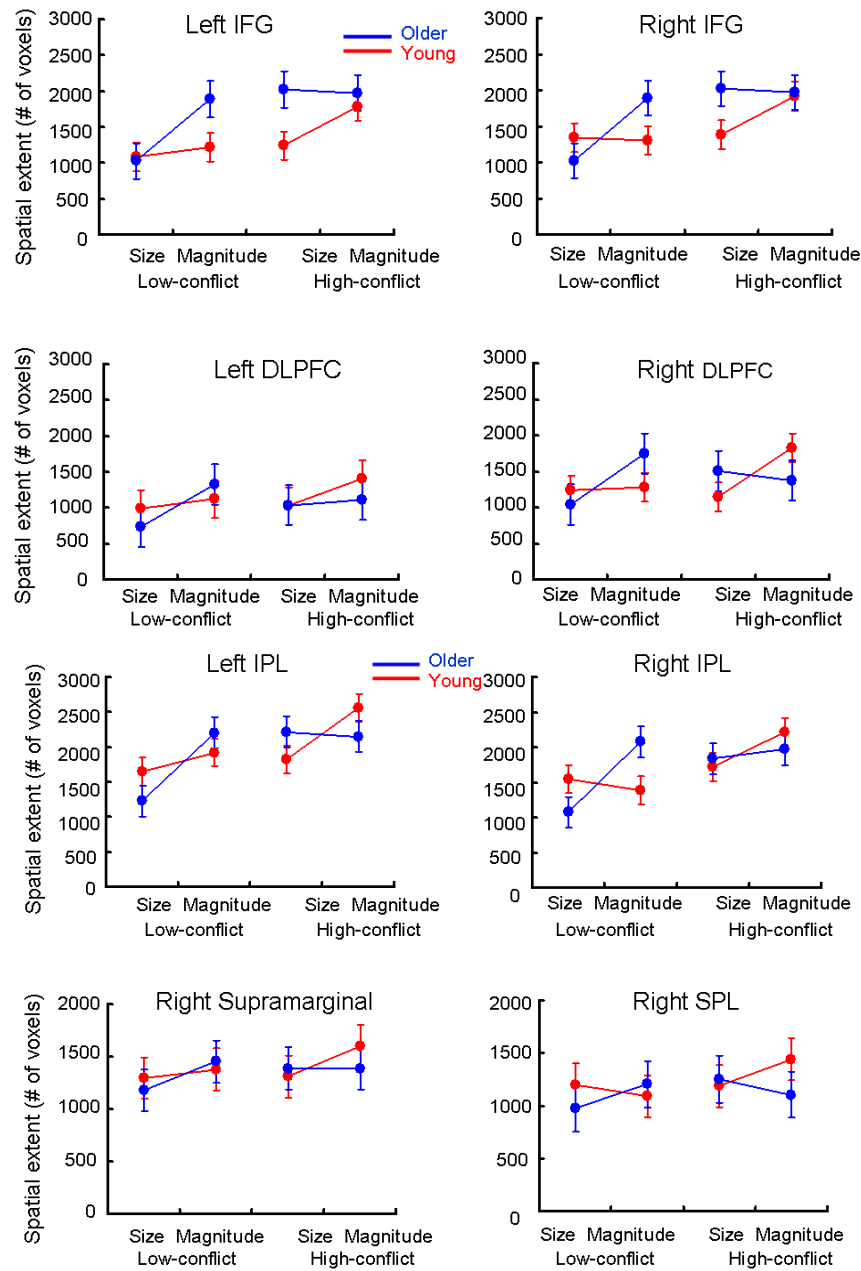
Figure 6. ROI analysis of the spatial extent of functional activation. The ROIs were selected from a prior study (see Methods). The ROIs include bilateral inferior frontal gyrus (IFG), bilateral dorsolateral prefrontal cortex (DLPFC), and bilateral inferior parietal lobule (IPL), right supramarginal region, right superior parietal lobule (SPL), anterior cingulate cortex (ACC), thalamus, and bilateral cerebellum for older (blue) and young (red) adults. Spatial extent was calculated using an uncorrected threshold of p<.001 for each participant and for each level of task demand.
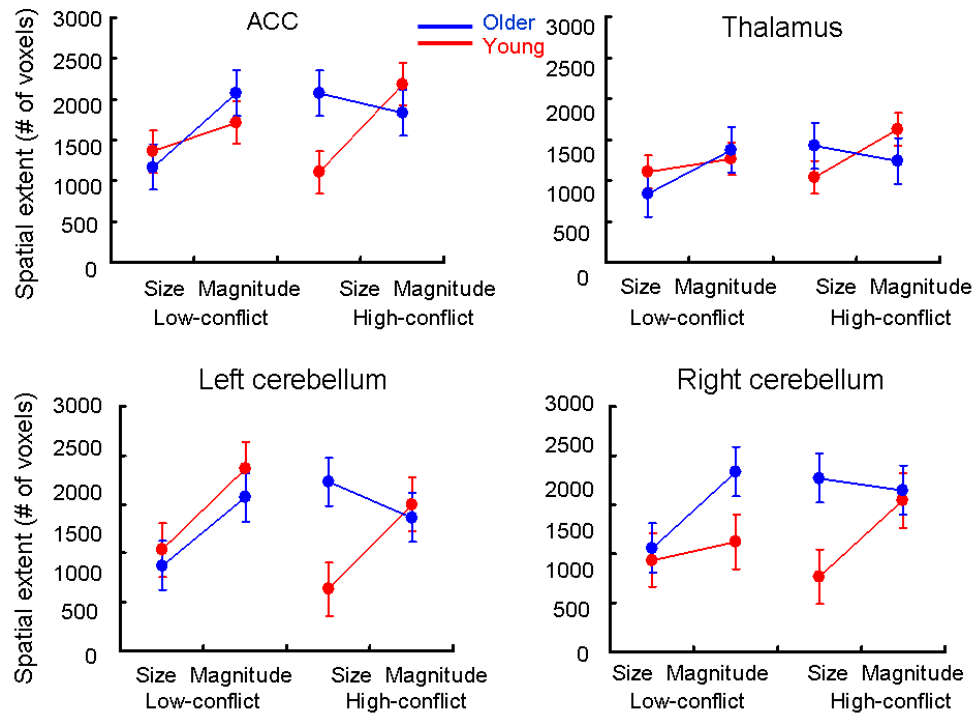
Figure 6 (cont.)
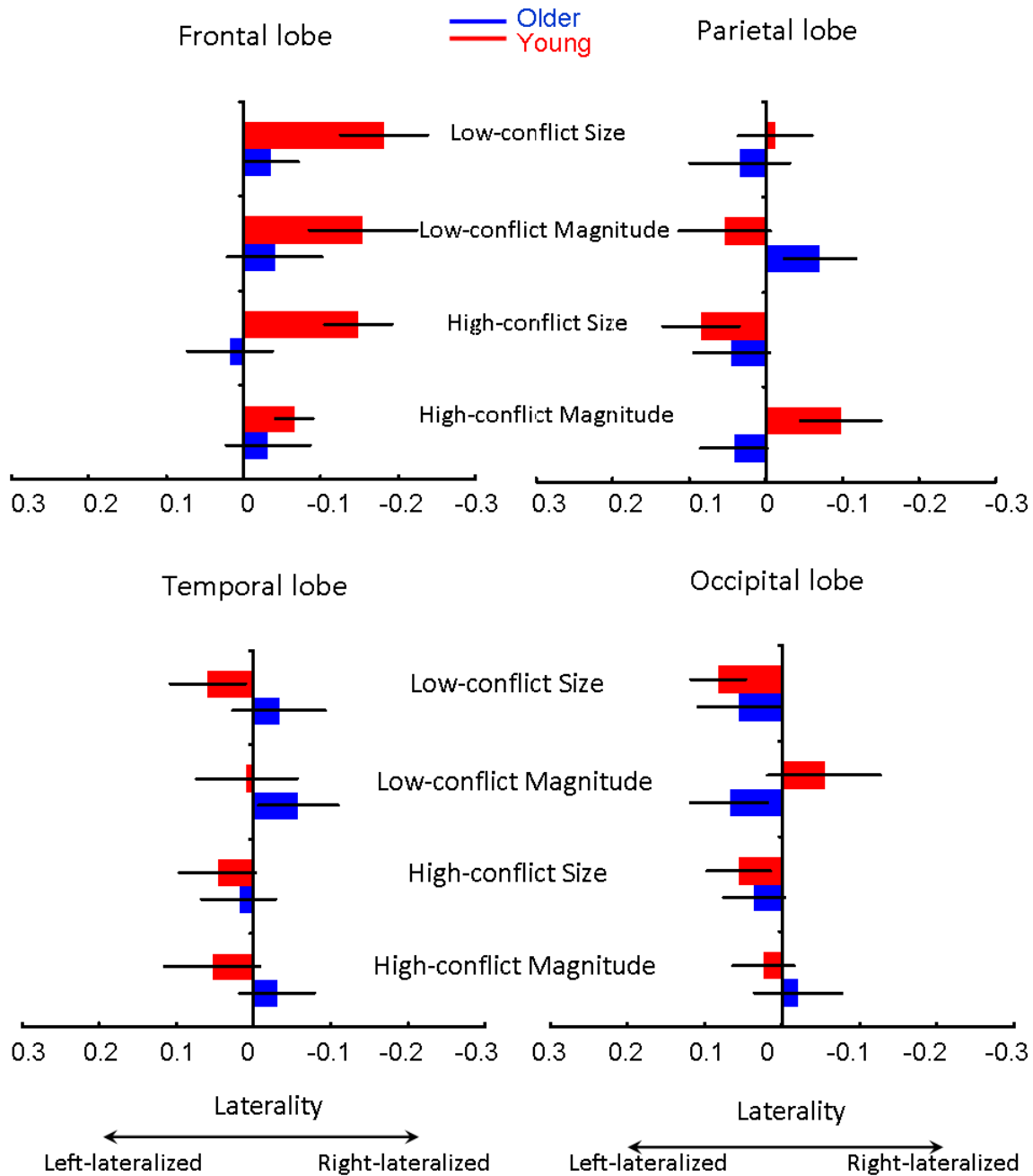
Figure 7. Laterality analyses of functional activation. The threshold-weighted values were computed over frontal, parietal, temporal, and occipital regions to indicate laterality of functional activation for young and older adults in each level of task demand. Laterality are computed according to: $[(\sum \text{voxel}_{left} - \sum \text{voxel}_{right})/(\sum \text{voxel}_{left} + \sum \text{voxel}_{right})]$, with laterality >0.1 for left-lateralized activation, laterality < -0.1 for right-lateralized activation, and values between 0.1 and -0.1 for bilateral activity.

THE EFFECTS OF AGING WHITE MATTER, COGNITIVE PERFORMANCE,

AND CORTICAL RECRUITMENT

Introduction

Evidence from cross-sectional and longitudinal studies in cognitive neuroscience of aging have demonstrated that biological aging is associated with reductions in white matter fiber integrity (Davis et al., 2009; Gordon et al., 2008; Gunning-Dixon & Raz, 2003; Sullivan, & Pfefferbaum, 2006; Sullivan et al., 2010). There is converging evidence that age-related reductions in white matter integrity have direct consequences for their cognitive performance. With regarding to processing speed, Madden et al. (2004) reported that reaction times of visual detection speed were associated with regional anisotropy of white matter integrity. Kennedy & Raz (2009c) recently found that slowed speed of cognitive processing was related to a reduced integrity in anterior white matter regions. These findings support the notion that general slowing in older adults may stem from degraded neural transmission along the axonal fibers of the aging brain. With regard to memory performance in retrieval, Kennedy & Raz (2009b) reported that reduced performance on a variety of memory tasks was correlated with age-related reductions in white matter microstructure in the internal capsule and superior parietal regions, suggesting that intact white matter across temporoparietal regions may contribute to memory performance in older adults.

Moreover, with regard to working memory, Charlton et al. (2006) first reported a significant correlation between working memory performance and white matter integrity,

with Digit-Symbol sequencing performance negatively correlated with the integrity in anterior, middle, and posterior portions of the aging brain. Zahr et al. (2009) further reported the linkage between working memory and corpus callosum, with poor working memory in older adults relating to less integrity of anterior portion of corpus callosum. Additionally, Kennedy & Raz, (2009b) found that poorer working memory in older adults appears to be associated with age-related reduction in white matter integrity in widespread networks of regions ranging from anterior (prefrontal, anterior corpus callosum) to posterior (termporal and occipital) regions of the brain. These DTI findings suggest that working memory performance appears to depend on white matter integrity in a widespread network of the aging brain.

Finally, with regard to the relationship between cognitive control and white matter integrity, increased task switching costs have been reported to associate with reduced integrity of frontoparietal white matter (Gold et al., 2010), integrity of prefrontal (Gratton et al., 2009), anterior corpus callosum, superior parietal, and occipital white matter (Kennedy & Raz, 2009b), as well as the genu of the corpus callosum (Madden et al., 2009). Also, higher Stroop interference cost were found to be associated with reduced anisotropy of the posterior white matter in older adults, particular in parietal, splenium, and occipital regions of the aging brain (Kennedy & Raz, 2009b). Some DTI studies, however, did not find significant association between Stroop interference cost and regional corpus callosum fiber (Sullivan & Pfefferbaum, 2006). More recently, Davis et al. (2009) using fiber tracking technique on young and older adults, they reported that greater white matter integrity in anterior regions but not posterior regions of the aging brain was related to better executive functioning. These results suggest that, congruent

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with the findings in working memory domain, performance of cognitive control in older adults appears to involve in white matter integrity in a widespread network of the aging brain.

Age-related changes in functional brain activity have been suggested to reflect neural scaffolding in response to age-related disruption in white matter integrity (Park & Reuter-Lorenz, 2009; Rodrigue & Kennedy, 2011). Thus far, only a few studies investigated the association between age-related reduction in white matter integrity and age-related changes in functional brain activity. In an initial work, Persson et al. (2006) combined DTI and fMRI techniques to index age-related memory decline in an incidental encoding task. They found that poor-performing older adults showed reduced white matter integrity in the anterior region of corpus callosum, and greater additional recruitment of right prefrontal cortex in a left-lateralized fMRI task. Another study combining DTI and fMRI tools, however, reported an opposite pattern. de Chastelaine et al. (2011) examined neural correlates of successful encoding in young and older adults. They found that age-related additional recruitment of the right prefrontal cortex in verbal memory encoding task was correlated positively with anterior callosal integrity and negatively with memory performance. More recently, Davis et al. (2011) investigated the association among accuracy, structural connectivity, and additional cortical recruitment using lateralized word matching task in young and older adults. Older adults showed positive correlation between white matter integrity of corpus callosum and performance, but no significant correlation between age-related additional cortical recruitment and white matter integrity of corpus callosum. These studies provide preliminary evidence that declined cognitive performance and differential cortical activation patterns are likely

due in part to reduced integrity of the white matter structural connectivity in the brains of older adults.

In the previous experiment, we demonstrated that older adults appear to have reduced capacity of recruiting more neural resources in response to increasing task demands during cognitive control. Given the impact of white matter integrity on cognitive performance and functional brain activation, an intriguing possibility is that an inability to modulate neural activity in older adults may stem from age-related changes in white matter integrity, particular in corpus callosum in which mediates the interhemispheric communication during demanding tasks to prevent interference from the opposite hemisphere (Bonzano et al., 2008; Eliassen et al., 2000). In the present experiment, we thus examined the influences of individual differences in white matter integrity, focusing on interhemispheric connectivity, on frontoparietal bilateral activation, and on behavioral performance in both young and older adults. The same participants from the previous experiment underwent another MRI technique involving the measures of white matter integrity after the fMRI experimental session. Fractional anisotropy (FA), a measure of the orientationally restricted diffusion of water by fibers, in anterior and posterior regions of callosal fibers was measured to assess the white matter integrity of each participant using Diffusion Tensor Imaging (DTI) technique.

Based on previous results in cognitive neuroscience of aging studies, we put forward two major hypotheses. On the one hand, the compensation hypothesis posits that age-related increases in brain activation, as well as the bilateral cortical recruitment, compensate for behavioral deficits (Cabeza 2002; Davis et al. 2011; de Chastelaine et al. 2011) such as inefficient inhibitory processes and/or compensate for age-related

neurodegeneration such as reduced medial temporal function (Cabeza et al., 2004; Gutchess et al., 2005; Park et al., 2003) and reduced visual processing (Cabeza et al., 2004; Davis et al., 2008; Goh et al., 2010). Although the compensation hypothesis does not clearly specify the effect of white matter integrity in corpus callosum on additional/bilateral cortical recruitment, we speculate that, age-related degradation in integrity of callosal fibers would jeopardize the compensatory "re-routing" of the information flow between two hemispheres and lead to a reduced bilateral pattern of brain activation. By this view, the compensation hypothesis would support the possibility that intact and/or greater integrity of white matter fibers along the corpus callosum predicts greater bilateral activation and improved task performance. Conversely, the pattern of unilateral activation and poor performance in older adults would stem from age-related disruption in white matter integrity of corpus callosum.

On the other hand, the detrimental nonselective hypothesis postulates that age-related declines in white matter integrity of corpus fibers (particular in anterior portion of the aging brain) result in impaired interhemispheric communication and a failure to select appropriate cortical processors for the given task, which in turn leads to additional/bilateral cortical recruitment (Logan et al., 2002; Persson et al., 2006) and reduced ability to efficiently inhibit task-irrelevant information (e.g., O'Sullivan et al., 2001), particularly under conditions of demanding executive/inhibitory control tasks (Colcombe et al., 2005; Milham et al., 2002; Nielson et al., 2002).

In the present experiment, we expect that, first, older participants would show reduced white matter integrity (i.e., lower FA) in corpus callosum compared to their young counterparts, consistent with previous research (Sullivan et al., 2006; Madden, et

al., 2009; Kennedy & Raz 2009b). Second, the greater effect of age would be observed in the anterior than in the posterior corpus callosum, indicating an anterior-to-posterior axis of increasing FA with age (Davis et al., 2011; Gordon et al., 2008; Gunning-Dixon & Raz, 2003; Sullivan, & Pfefferbaum, 2006; Sullivan et al., 2010). Finally, with regard to the effect of white matter integrity on age-related cortical recruitment and task performance, reduced integrity of callosal fibers would result in greater bilateral cortical recruitment and couple with declined task performance in older adults, in keeping with the detrimental nonselective hypothesis. In contrast, reduced integrity of callosal fibers would yield decreased bilateral cortical recruitment and relate to declined task performance in older adults, as the compensation hypothesis suggested.

Methods

Participants

These were the same participants as in Experiment 1. A total of 15 young adults (mean age = 25.5 years, ages 21-32 years; 9 females) and 15 healthy community-dwelling older adults (mean age = 65.6 years, ages 61-72 years; 6 females) participated in the study. The study was approved by the University of Illinois at Urbana-Champaign institutional review board and all participants gave informed consent prior to their participation. Participants were physically and cognitively healthy, right-handed individuals with no counter-indications for MRI scanning, and were remunerated for their participation. The DTI data in two young participants were unusable due to technical reasons.

Imaging Acquisition

MRI scans were conducted on a 3T Siemens Allegra system with a single-channel head coil (Siemens, Erlangen, Germany) at the University of Illinois at Urbana-Champaign. Diffusion Tensor Imaging (DTI) images were acquired for each participant with a single-shot EPI sequence with 32 slices, voxel size 3.4375 x 3.4375 x 4mm, field of view (FOV) 220 x 220mm, matrix size 64 x 64, TR = 4800ms, b-value = 1000s/mm2. Diffusion gradients were applied in thirty directions. Four reference images were acquired and averaged.

Data Analyses

Behavior

To assess individual differences in in-scanner task performance, a proportional interference percentage was computed for each participant according to individual's reaction times (RT) using the following formula:

$$\text{Interference (\%)} = [(\text{RT}_{\text{high-conflict}} - \text{RT}_{\text{low-conflict}}) / \text{RT}_{\text{low-conflict}}] * 100$$

This computation has been used in a variety of aging fMRI studies in order to control for generally slower reaction time in older adults (Colcombe et al. 2005; Langenecker et al., 2004). Larger positive interference percentages indicate greater interference and values around 0 indicate the absence of interference.

Diffusion Tensor Imaging

Diffusion-weighted data were separately processed for each participant using FSL

(http://www.fmrib.ox.ac.uk/fsl) processing streams and custom MATLAB scripts (MATLAB, R2008; MathWorks Inc., Natick, MA). From the diffusion tensor, three eigenvectors that define the direction of the diffusion system can be determined by diagonalizing the tensor for each voxel. The eigenvalues $\lambda 1$, $\lambda 2$, and $\lambda 3$, which correspond to the three eigenvectors, represent the magnitude of diffusivity in the three directions. Based on these three diffusivities, fractional anisotropy (FA), were then calculated. Each participant's average $b = 0$ image was coregistered with their high-resolution image using Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, UK), and the resulting transformation was applied to the FA image. Voxel-wise FA values range from 0 to 1 (0, isotropic diffusion; 1, maximum anisotropy) and FA maps were created. Therefore, higher FA values can be interpreted as reflecting higher white matter integrity and may be related to myelination levels along the axonal fibers, resulting in more efficient conduction of neural signals and better transmission of information across the brain (Song et al., 2002; for review, see Sullivan & Pfefferbaum, 2006).

For each participant, regions of interest (ROIs) were drawn directly onto axial slices of the FA maps to cover the full extent of the anterior and posterior corpus callosum separately (Hofer & Frahm, 2006). Each participant's FA values were then averaged across all identified slices in each of the ROIs to yield single value for the anterior and posterior regions of the corpus callosum. The values of FA were analyzed with a 2 x 2 ANOVA with age (young adults, older adults) as a between-subject factor and callosal region (anterior, posterior) as a within-subject factor.

fMRI: Laterality Analyses

To assess individual differences in bilateral cortical recruitment, the threshold-weighted laterality indices indicating laterality of functional activation over inferior frontal gyrus (IFG) and posterior parietal cortex (PPC) for each participant and each level of task demand were calculated. The IFG and PPC were identified in automated anatomical labeling (AAL, Tzourio-Mazoyer, et al., 2002) provided with SPM software to yield anatomically-defined masks to be used in laterality analysis.

Laterality indices were based on the standard formula (Everts et al., 2009):

$$\text{Laterality} = [(\Sigma\text{voxel left} - \Sigma\text{voxel right}) / (\Sigma\text{voxel left} + \Sigma\text{voxel right})]$$

This formula results in positive values for predominantly left-lateralized activity (laterality > 0.1), negative values for predominantly right-lateralized activity (laterality < -0.1), and values between 0.1 and -0.1 for bilateral activity (Everts et al., 2009; Powell et al., 2012). To ensure the findings laterality differences in these regions were not due to the significance threshold selected for analyzing fMRI data (Cabeza 2002), we computed laterality indices using boostraping approach (Wilke & Schmithorst, 2006).

Results

Behavioral Results: Interference Percentage

Interference percentage was computed for each participant and each task to assess individual differences in task performance. In the Size task, the values of interference percentage for young and older adults are 11.9 and 16.2, respectively. In the Magnitude task, the values of interference percentage for young and older adults are 19.5 and 21.1,

respectively. Although older adults have larger values of interference percentage, we did not find significant effect of age in the Size (t = 1.10, p =0.15) and the Magnitude tasks (t = 0.72, p = 0.24). The results were consistent with the behavioral results presented in Experiment 1 (see Table 2) and indicated that older adults showed equivalent in-scanner task performance with young adults despite older adults revealed general slowing in response times.

DTI Results

A 2 x 2 ANOVA with age (young adults, older adults) as a between-subject factor and callosal region (anterior, posterior) as a within-subject factor on FA values yielded a significant effect of age [F(1, 56) = 6.77, p< 0.05]: older adults have significantly lower integrity of anterior as well as posterior portions of corpus callosum than young adults (Fig. 8). There was no significant effect of region on FA values [F(1,56) = 1.43, p = 0.24]. Moreover, age did not significantly interact with region [F(1, 56) = 0.52, p = 0.47].

Associations between White Matter Integrity and Behavioral Performance

To examine the associations between white matter integrity and task performance, the correlation analyses linking regional microstructural integrity of white matter (i.e., FA values in anterior and posterior regions of the corpus callosum) to individuals' in-scanner behavioral performance (interference percentages) for each task were performed. These correlations were computed for the young and older group separately and for the two groups combined (Reuter-Lorenz et al., 2000).

Consistent with previous research (Gratton et al., 2009; Kennedy & Raz, 2009b; Madden et al., 2009; Davis et al., 2009), we found a significantly positive correlation

between performance and FA values of corpus callosum in older adults. Specifically, older adults displayed that greater FA values in anterior corpus callosum were associated with smaller interference percentage (i.e., better performance) in the Size ($r = -0.73$, $P < .01$) and the Magnitude ($r = -0.56$, $P < .05$) tasks, and moreover, greater FA values in posterior corpus callosum were associated with smaller interference percentage in the Size task ($r = -0.57$, $P < .05$) (and marginally significant in the Magnitude task, $r = -0.49$, $P = .06$). For young adults, however, we found that greater FA values in anterior but not in posterior corpus callosum were associated with smaller interference percentage (i.e., better performance) in the Size and the Magnitude tasks (Anterior: Size task, $r = -0.66$, $P < .05$; Magnitude task, $r = -0.88$, $P < .01$; Posterior: Size task, $r = -0.22$, $P = 0.47$; Magnitude task, $r = -0.41$, $P = 0.16$) (Table 7).

Additionally, the analysis for the two groups combined showed a significantly negative correlation between performance and FA values of corpus callosum, with both anterior and posterior corpus callosum were associated with smaller interference percentage (i.e. better performance) across two tasks (Anterior: Size task, $r = -0.71$, $P < .01$; Magnitude task, $r = -0.59$, $P < .01$; Posterior: Size task, $r = -0.45$, $P < .05$; Magnitude task, $r = -0.39$, $P < .05$). These findings suggest that anterior portion of corpus callosum is critical for both young and older adults during demanding cognitive control task, and more importantly, older adults appear to depend more on posterior portion of white matter callosal integrity of the aging brain than their young counterparts, which we speculate a compensatory process in order to maintain optimal task performance.

Associations between White Matter Integrity and Bilateral Cortical Recruitment

To examine the role of white matter integrity on age-related cortical recruitment, the correlation analyses between regional microstructural integrity of white matter (i.e., FA values in anterior and posterior regions of the corpus callosum) and individual's laterality of functional activation over inferior frontal gyrus (IFG) and posterior parietal cortex (PPC) for each level of task demand were performed. We are aware that anterior and posterior corpus callosums are responsible for carrying white matter fibers connecting cross-hemispheric frontal and parietal cortices, respectively; we thus performed separately correlation analyses linking integrity of anterior corpus callosum to laterality of IFG activation and linking integrity of posterior corpus callosum to laterality of PPC activation. In addition, such correlations were computed for the young and older group separately and for the two groups combined.

As summarized by Table 7, we found significantly negative correlations between FA values of anterior corpus callosum and laterality of functional activity in IFG for young adults but not older adults, particular in higher levels of task demand. Specifically, whereas young adults revealed that greater integrity of anterior corpus callosum was associated with more bilateral IFG activation in higher levels of task demand (high-conflict Size condition: r = -0.61, P < .05; high-conflict Magnitude condition: r = -0.53, P =0.06), older adults did not show this relationship with increasing task demands (high-conflict Size condition: r = -0.37, P = 0.17; high-conflict Magnitude condition: r = -0.05, P =0.87) as illustrated by Fig. 9. Additionally, when correlation was computed for the two groups combined, greater FA values of anterior corpus collasum were associated with more bilateral IFG activation in higher levels of task demand (high-conflict Size

condition: r = -0.46, P <.05; high-conflict Magnitude condition: r = -0.32, P =0.09),

suggesting a critical role of anterior corpus callosum for recruiting alternative neural

resources of frontal region in response to demanding tasks across the lifespan.

With regard to the association between FA values of posterior corpus callosum and

laterality of PPC activity, we found differential patterns of associations for young and

older adults. As summarized by Table 7 and illustrated in Fig. 10, young adults displayed

significantly negative correlation between FA values of posterior corpus callosum and

laterality of PPC activation in low-conflict Magnitude condition (r = -0.69, P <.01) but

positive correlation between FA values of posterior corpus callosum and laterality of PPC

activation in high-conflict Magnitude condition (r = 0.59, P <.05). Specifically, greater

integrity of posterior corpus callosum in young adults was associated with more bilateral

PPC activation in low-conflict condition, but with more unilateral activation in

high-conflict condition for the Magnitude task, probably reflecting a task-specific manner

of neural recruitment for controlling processes in physical-numerical interference

paradigm (Huang et al., 2012; Kaufmann et al., 2005; Liu et al., 2006; Tang et al., 2006).

In contrast, older adults showed a negative correlation between FA values of posterior

corpus callosum and laterality of PPC activation in high-conflict Size condition (r = -0.61,

P <.05), with greater integrity of callosal fibers for more bilateral pattern of PPC

activation.

Discussion

We provide evidence that individual differences in micro-structural integrity of

white matter, particular in corpus callosum, relate to both bilateral cortical recruitment

and task performance in young and older adults. We found that greater integrity of anterior callosal fibers in individuals was associated with more bilateral frontal activation in higher levels of task demand and associated with better performance across tasks, indicating a critical role of anterior corpus callosum for recruiting additional neural resources of frontal regions in response to increasing task demands across the lifespan. Moreover, despite the fact that older adults on average revealed lower integrity in both anterior and posterior portions of corpus callosum than young adults, greater integrity of posterior corpus callosum was related to better performance indexed by interference percentage for older adults but not young adults (see Table 7). Older adults, however, did not show association between integrity of anterior corpus callosum and laterality of IFG activation with increasing task demands, whereas young adults displayed a more bilateral pattern of IFG activation coupling with greater integrity of anterior callosal fibers in higher levels of task demand, suggesting that age-related degradation in white matter integrity of anterior corpus callosum may be a contributing factor of reduced capacity to modulate neural resources in response to increasing task demands in older adults.

The observed pattern of relations supports the possibility that regional degradation of white matter fiber integrity may be a critical source of age-related functional compromise and may limit the capacity to recruit alternative neural systems to compensate for cognitive declines. Although our results seems to support the compensation hypothesis which posits that age-related bilateral cortical recruitment is displayed to compensate for cognitive declines and neural deficits, we do note that the data should be carefully interpreted. For example, the compensation hypothesis may point that age-related bilateral cortical activation could compensate for a reduced integrity of

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anterior corpus callosum in older adults because of a significant correlation between the laterality of functional activation and white matter integrity of corpus callosum. However, it seems very unlikely to conclude this because the corpus callosum itself mediates the inter-hemispheric cortical recruitment in response to changing task demands. In other words, integrity of callosal fibers may be the *causes* rather than the *target* of observed age-related bilateral cortical recruitment.

Consistent with previous works (Davis et al., 2011; Gordon et al., 2008; Head et al., 2004; Gunning-Dixon & Raz, 2003;; Kennedy & Raz, 2009a; Sullivan, & Pfefferbaum, 2006), lower integrity of anterior and posterior callosal fibers were observed in older adults compared to young adults in the present study (see Fig. 8). We further reported that, in addition to the beneficial effect of anterior corpus callosim, posterior corpus callosum appears to be supportive of task performance in older adults, with greater integrity of posterior corpus callosum associating with smaller effect of interference during executive controlling processes. Similarly, Kennedy & Raz, (2009b) also reported that a higher Stroop interference cost was associated with reduced anisotropy of the posterior white matter in older adults, particular in parietal, splenium, and occipital regions of the aging brain. Along these lines, our results of fMRI-DTI correlation analyses also found that greater integrity of posterior corpus callosum in older adults was related to more bilateral pattern of functional activation in parietal regions in high-conflict Size condition, which we interpret as an attempt of recruiting alternative neural resources to maintain the allocation of attention.

Some intriguing results were observed when the association between DTI measure, behavioral measures, and fMRI measures were performed for the two age groups

combined. Regarding DTI-behavior association, the integrity of anterior and posterior corpus callosum was significantly related to individual's performance in both the Size and the Magnitude tasks, with reduced white matter integrity of corpus callosum coupling with impaired performance for individuals. This result highlights that individual differences rather than age differences in integrity of callosal fibers may be a contributing factor to an individual's task performance. Moreover, fMRI-DTI results demonstrated that individual's greater integrity of anterior callosal fibers was reliably associated with more bilateral frontal activation in higher levels of task demand, suggesting that individual differences in bilateral pattern of functional activation with increasing task demands may stem from the individual differences in integrity of white matter fibers. These findings, congruent with our observations in the previous fMRI study, suggest a lifespan continuity of white matter integrity of corpus callosum as well as bilateral recruitment of neural activation (Fabiani et al., 2012; Hedden & Gabrieli, 2004). In other words, functional brain activation and structural brain variations appear to be gradual rather than abrupt as a function of aging.

In conclusion, the cumulative evidence from this DTI and previous fMRI studies suggest that older adults have reduced or limited capacities of recruiting more neural resources in response to increasing task demands. Such reduction appeared to be associated with age-related degradation in white matter integrity, particular in corpus callosum, which mediates the inter-hemispheric cortical recruitment in response to changing task demands. Moreover, we also highlight the importance of individual differences on behavioral, functional and structural changes across the lifespan.

Table 7. Correlations between DTI measures (indexed as FA value of anterior and posterior portions of corpus callosum), behavioral measures (indexed as interference percentage), and functional MRI measures (indexed as laterality index) in young and older adults.

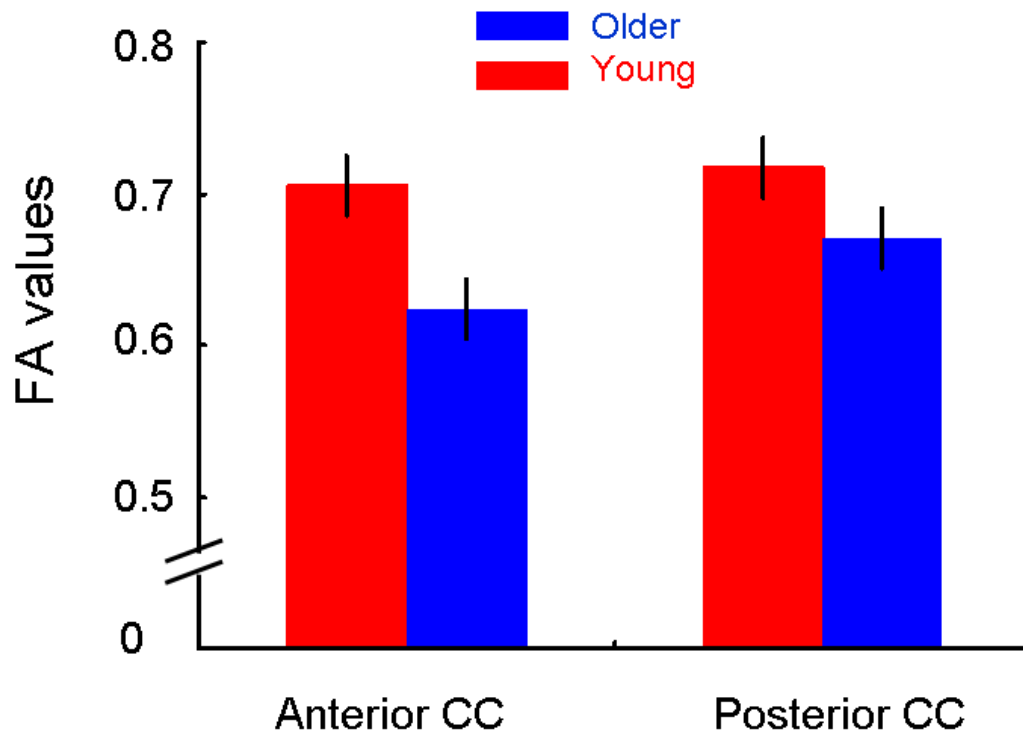|	Anterior FA			Posterior FA		
	Young	Older	All	Young	Older	All
Behavioral measures: Interference percentage						
Size task	-0.66**	-0.73***	-0.71***	-0.22	-0.57**	-0.44**
Magnitude task	-0.88***	-0.56**	-0.59***	-0.40	-0.49*	-0.38**
fMRI measures: Laterality index						
Inferior frontal gyrus						
Low-conflict Size	-0.28	0.47*	0.29			
Low-conflict Mag	0.09	-0.11	-0.02			
High-conflict Size	-0.61**	-0.37	-0.46**			
High-conflict Mag	-0.53*	-0.05	-0.32*			
Posterior parietal cortex						
Low-conflict Size				-0.11	0.44	0.07
Low-conflict Mag				-0.69***	-0.12	-0.19
High-conflict Size				-0.14	-0.61**	-0.29
High-conflict Mag				0.59**	-0.31	0.22

*p< .1; **p < .05; ***p < .01.

Figure 8. White matter integrity of anterior and posterior corpus callosum (CC) for young and older adults. Fractional anisotropy (FA) values were scaled from 0 to 1 (0, isotropic diffusion; 1, maximum anisotropy). Higher FA values reflect higher white matter integrity.
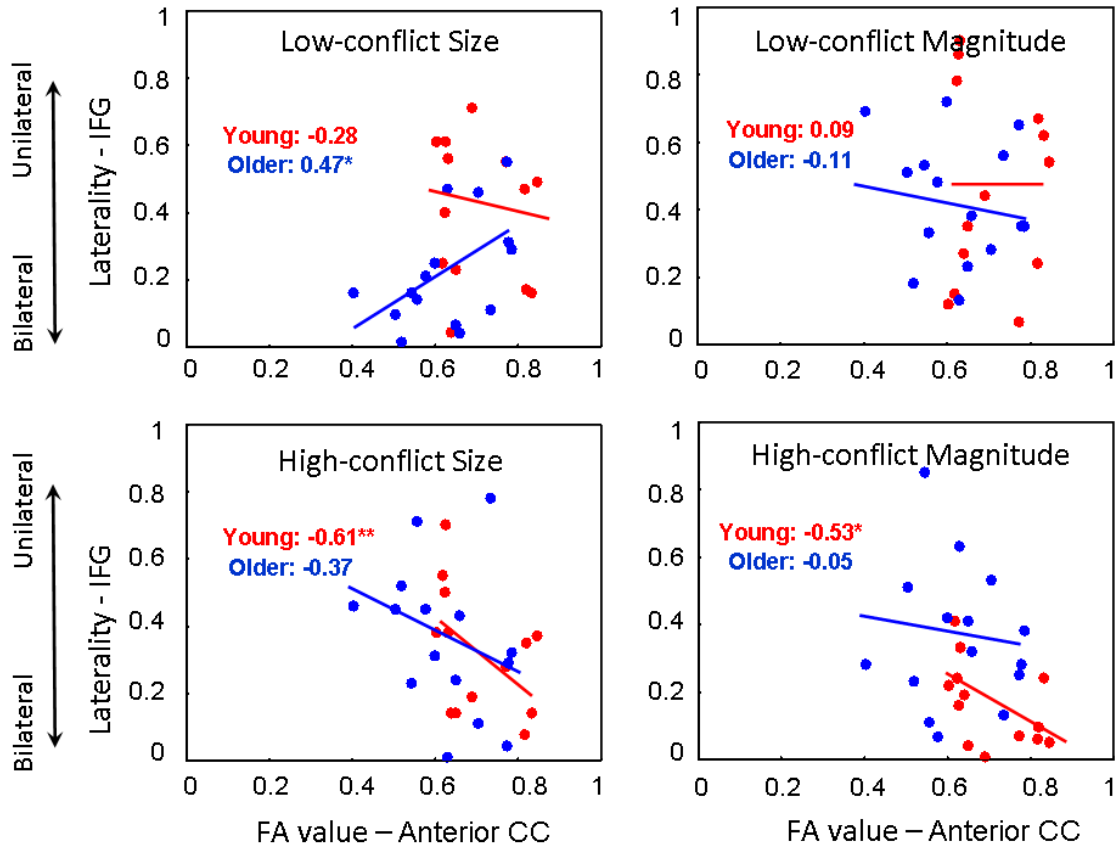
Figure 9. Relationship of white matter integrity of anterior corpus callosum (CC) and laterality of inferior frontal gyrus (IFG) activation for young and older adults and for each levels of task demand. FA values in anterior corpus callosum and laterality of functional activation over inferior frontal gyrus were computed for each participant under each level of task demand (low-conflict Size condition, low-conflict Magnitude condition, high-conflict Size condition, and high-conflict Magnitude condition).

Figure 10. Relationship of white matter integrity of posterior corpus callosum (CC) and laterality of posterior parietal cortex (PPC) activation for young and older adults and for each levels of task demand. FA values in posterior corpus callosum and laterality of functional activation over posterior parietal cortex were computed for each participant under each level of task demand (low-conflict Size condition, low-conflict Magnitude condition, high-conflict Size condition, and high-conflict Magnitude condition).
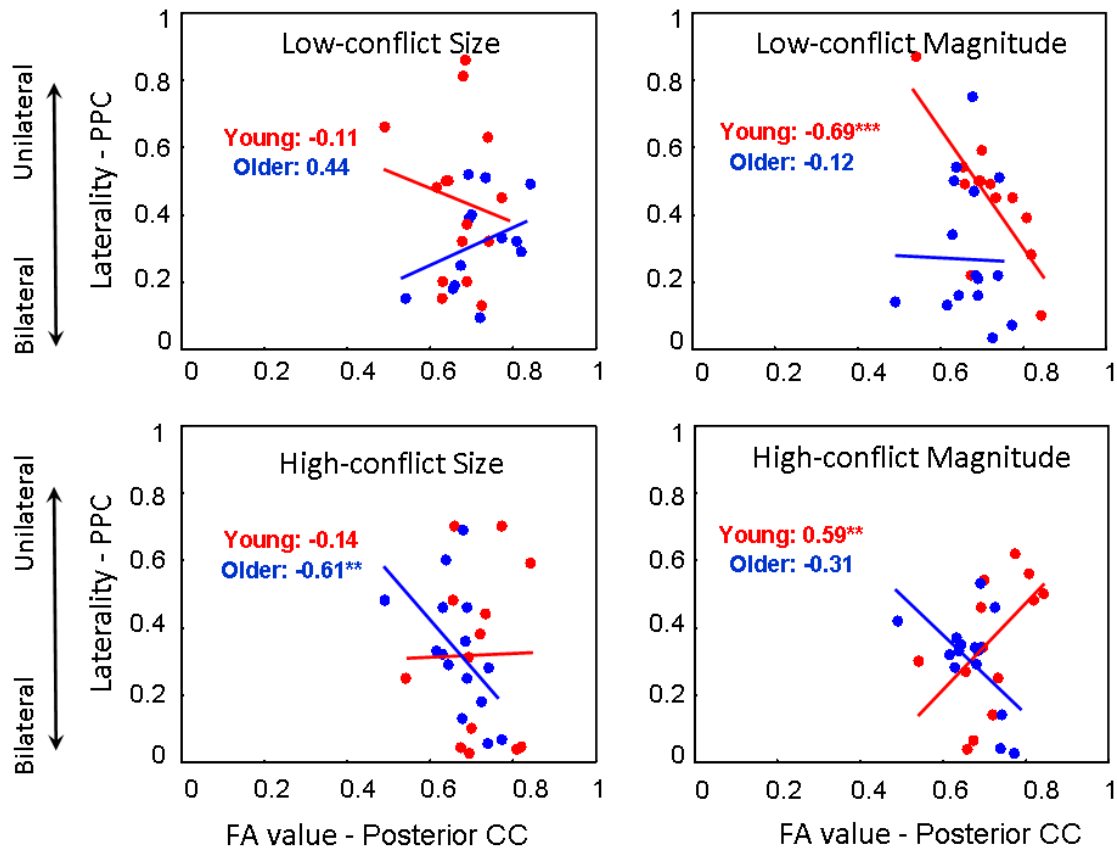
CHAPTER 4

THE EFFECTS OF AGE AND CULTURE ON CORTICAL RECRUITMENT

Introduction

While functional and structural characteristics of the brain are largely influenced by biological aging, there is growing evidence demonstrating that differences in external experience and sustained practice such education, training, and aerobic exercise also impact neural organization in function and structure (Ansari, 2012; Chee et al., 2010; Draganski et al., 2004; Erickson et a., 2007; 2011; Kramer et al., 2005; Maguire et al., 2000; Wiesmann & Ishai, 2010). Understanding how such variations in neural organization arise between different individuals over the human lifespan is important for uncovering factors that influence developmental trajectories from adulthood to advanced age. In this study, we consider two general sources that contribute to neural function over the adult lifespan – age-related biological changes and culture-related differences in external experience.

The evidence describing earlier in Introduction section indicated that there are subtle differences in the way individuals process information that appears to be a product of cultural experiences. Westerners, due to the individualistic, independent, and self-based focus of their culture, have a tendency to process focal objects and organize information via rules and categories in an analytic way. In contrast, East Asians, based on their collectivist and interdependent representation, tend to view themselves as part of a larger whole, resulting in a holistic information-processing bias in which relational/functional information is prioritized over categorical information (Goh & Park, 2009; Kitayama &

Uskul, 2011; Masuda & Nisbett, 2001; Nisbett & Masuda, 2003; Park & Huang, 2010). It is worth pointing that cultural experience is unique in that it encompasses a lifetime and highly reinforced influence rather than aerobic exercise (Erickson et a., 2009) or practices like juggling (Draganski et al., 2004) which may not be as frequent and have shown reversal of effects if stopped (e.g., Draganski et al., 2004). Over the lifespan, both neurobiological (i.e. aging) and experiential (i.e., culture) factors appear to continuously and jointly shape cognition and influence neural function (Park, Nisbett, & Hedden, 1999; Park & Gutchess, 2002, 2006; Park & Huang, 2010). The goal of this experiment is to evaluate the effects of lifespan factors of culture and aging, in terms of how different cultural experiences modulate the pattern of age-related cortical recruitment. Specifically, we investigated whether observed bilateral pattern of functional activation in older adults is ubiquitous across individuals who grew up in different cultural backgrounds. To address this issue, we focused on semantic categorization task, in which has been demonstrated cultural differences in behavior and showed differential pattern of cortical recruitment for young and older adults in a sample of Western subjects.

There is evidence that cultural experiences impact how semantic information is used and organized (Chiu, 1972; Choi et al.1997; Nisbett et al. 2001; Ji et al. 2004). For example, in a semantic judgment task, Ji et al. (2004) reported that East Asians and Westerners showed differences in their organization of categorical information. They found that Westerners tend to relate pairs of items by rules and categories (e.g., "cow, horse") whereas East Asians are biased towards relating pairs on the basis of relationships and functional features (e.g., "cow, grass"), suggesting a categorical-related and a functional-sensitive processing style for Westerns and East Asians.

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Recently, using a modified version of semantic judgment task from Ji et al. (2004), Gutchess et al. (2010) acquired fMRI data as Western and East Asian young adults made categorical and functional relationship judgments for triads of English words in the scanner. They found that, across both categorical and functional relationship judgments, East Asians activated a fronto-parietal network implicated in controlled executive processes, whereas Americans engaged regions of the temporal lobes, possibly in response to conflict semantic information (Gutchess et al. 2010). These findings indicate that cultural variation in the strategies was employed to resolve conflict between competing semantic judgments (Gutchess et al. 2010). More interestingly, for categorical relationship judgments, Gutchess et al. (2010) reported a more bilateral pattern of neural activation in prefrontal regions for East Asians compared to Westerners. The authors suggested that, whereas semantic and language-based tasks tend to predominantly engage left hemisphere regions, such overwhelmingly bilateral pattern of activation for cultural differences could reflect a more demanding condition for East Asians. In fact, the observed bilateral pattern of activation for East Asians in Gutchess et al. (2010) is congruent with the notion that individuals require greater effort when engaging culturally-non-preferred processing style (Hedden et al., 2008; Goh et al. 2011). By this view, East Asians may display more bilateral activation than Westerners in order to maintain their optimal performance during categorical relationship judgments because such task is associated with the processing style preferred by Westerners (i.e., categorical-related processing style).

Semantic categorical task is a typical verbal task that has been widely used in the imaging literature to investigate the effect of age (Andrews-Hanna et al. 2007; Logan et

al. 2002; Lustig & Buckner, 2004). In this task, older adults typically elicit greater bilateral activity than the more left-lateralized activity observed in their young counterparts, particular in prefrontal cortex (Bookheimer et al. 2002). Such age-related pattern of bilateral activation may be part of compensatory response, in particular for maintaining optimal performance in older adults. Given the evidence in Gutchess et al. (2010) demonstrating that East Asians appear to display a more bilateral pattern of prefrontal activation in a categorical judgment task, semantic categorization task appears to provide a means of comparing groups differences in the degree of laterality of functional activity across age and culture. Therefore, in the present study, we conducted a simple blocked fMRI experiment while young and older East Asian and Western participants performed a semantic categorization task. They were asked to make a button response to classify visually presented words as living or nonliving objects. Given the evidence in our previous experiment showing that older adults have reduced or limited capacities of recruiting more neural resources in response to increasing task demands, we did not manipulate different levels of task demand in this experiment to keep task demands objectively comparable between two age groups.

To the extent that semantic categorization task is preferred by Western processing style (Chiu, 1972; Nisbett et al. 2001; Ji et al. 2004), we expected East Asians to show greater bilateral activation during semantic categorization task indicating more cognitive effort for East Asians compared to Westerners to access categorical information. To the extent that recruiting additional neural resources is for optimal performance, we expected older adults to display more bilateral activation during semantic categorization task suggesting that more alternative resources were engaged for older adults than young adult

to process semantic knowledge.

Additionally, with respect to the interaction between age and culture on the pattern of cortical recruitment, three possible cases we described earlier in Introduction section would arise. First, to the extent that culture-related difference across individuals may accentuate with increasing age, we expected cultural difference observed in older adults to display a greater degree of bilaterality than cultural difference observed in young adults indicating that prolonged cultural exposure may result in engrained processing biases. Second, to the extent that culture-related differences may remain at the same level throughout the lifespan, we expected cultural difference observed in older adults to display an equivalent degree of bilaterality as cultural difference observed in young adults suggesting that cultural experience may reach an asymptotic level of influence on neurocognitive processing. Finally, to the extent that culture-related neural differences may be reduced with increasing age, we expected cultural difference observed in older adults to display a reduced degree of bilaterality as cultural difference observed in young adults indicating that global nature of age-related neurobiological changes impact all individuals who grew up in different cultural backgrounds

Methods

Participants

One hundred and ninety-one healthy right-handed participants with normal or corrected visual acuity were recruited in this fMRI study. There were 50 Young Americans (25 males, mean age: 22.1, range 20-29), 47 Young East Asians (25 males,

mean age: 24.2, range 20-30), 48 Older Americans (18 males, mean age: 66.5, range

61-78), and 46 Older East Asians (21 males, mean age: 66.1, range 61-76). East Asians

were Chinese Singaporeans (SG) recruited from local universities and communities in

Singapore. Westerners were American students (US) from the University of Illinois at

Urbana-Champaign, USA, and community residents around the university. Participants

underwent healthy screening and neuropsychological testing at a separate session and

were remunerated for both MRI scanning and behavioral testing. All had a minimum

score of 26 on the Mini-Mental State Examination (MMSE), indicating generally intact

cognitive functioning, especially for older adults. All participants also completed the

Schwartz Value Survey (SVS; Schwartz, 1992) that measures the degree to which they

subscribed to individualistic (Power, Achievement, Hedonism, Stimulation, and

Self-Direction) and collectivistic (Universalism, Benevolence, Tradition, Conformity, and

Security) values.

Experimental Material and Design

In this blocked-design fMRI experiment, all participants were presented with the

same set of 64 English-word stimuli (English is the official language in Singapore despite

the maintenance of a rich Asian culture) and instructed to indicate whether words

represented living or nonliving. Each word was displayed for 3 s followed by a 500 ms

fixation. There were eight words in each of eight semantic categorization blocks which

were alternated with eight control blocks which consisted of a fixation-cross (baseline

condition), all presented in a single run. Within each semantic categorization block, half

of words were non-living objects whereas the other half was living objects. Stimuli were

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presented using E-Prime software with back-projection through the scanner bore and a mirror mounted on the head coil.

Imaging Acquisition and Preprocessing

Functional images of the brain were acquired using two identical 3T Siemens scanner systems located in Singapore and Illinois, USA. Extensive tests between the two sites indicated that the functional signals obtained for this study were comparable between the two magnets (Sutton et al., 2008). 32 axial slices with 4 mm thickness were acquired using an EPI sequence with TR/TE =2s/32ms, FOV=220 x 220 mm. Co-planar structural T2 images were acquired to register and overlay the functional images to a 3D-MPRAGE T1 structural image.

Functional images were analyzed using SPM5 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) implemented in MATLAB version 7.0 (The MathWorks, Natick, MA, USA). The images were preprocessed with slice-time and motion correction, and normalized to MNI space. Images were then smoothed with a FWHM 8mm Gaussian kernel. In the first-level voxel-by-voxel statistical analysis, general linear models (GLM) were computed for each participant that consisted of the onsets of each of the semantic categorization and control blocks convolved with the hemodynamic response function, along with motion correction parameters.

Data Analyses

Behavioral performance, Neuropsychological test, and Schwartz Value Survey

The accuracy and reaction times (RTs) were analyzed with 2 x 2 design analysis of

variances (ANOVAs) with Cultural Group (US, SG) and Age (young adults, older adults) as between-subject factors.

The neuropsychological test includes three measures of processing speed: pattern matching, the Wechsler (WAIS-R) Digit-Symbol, and do matching, two measures of working memory: the Wechsler Memory Scale (WMS-III) Corsi Blocks Forward and Backward, and Letter-number Sequencing, and one measure of mental control: the WMS-III Mental Control Task. Each measure of cognitive tasks was analyzed with a 2 x 2 design ANOVA with Cultural Group (US, SG) and Age (young adults, older adults) as between-subject factors.

The Schwartz Value Survey measures the degree to which they subscribed to individualistic (Power, Achievement, Hedonism, Stimulation, and Self-Direction) and collectivistic (Universalism, Benevolence, Tradition, Conformity, and Security) values. Each value was analyzed with a 2 x 2 ANOVA with Cultural Group (US, SG) and Age (young adults, older adults) as between-subject factors.

fMRI: Whole brain Analyses

Functional images were analyzed using SPM5 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) implemented in MATLAB version 7.0 (The MathWorks, Natick, MA, USA). The images were preprocessed with motion correction and then normalized to MNI space. Images were then smoothed with a FWHM 8mm Gaussian kernel. In the first-level voxel-by-voxel statistical analysis, general linear models (GLM) were computed for each participant that consisted of the onsets of each of the semantic categorization and control blocks convolved with the

hemodynamic response function, along with motion correction parameters.

These individual response estimates were then used as the dependent variable in a second group-level analysis consisting of a 2 x 2 ANOVA with Age (older adult, young adult) and Cultural Group (US, SG) as between-subject factors. Group-level whole brain contrasts were then performed on the factorial model to identify voxels that showed significant effects of interest in the brain responses to the semantic categorization vs. control conditions.

To identify common brain responses to the semantic categorization vs. control conditions across groups, we performed a whole brain conjunction analysis across four groups (age and culture). We first identified regions that were significantly more active for the semantic categorization vs. control contrast in each group separately. We then intersected the four maps to identify regions that were significantly more active in semantic categorization vs. control contrast. For this conjunction analysis, we used a threshold of p < .001 with an extent threshold of 10 contiguous voxels.

fMRI: Region-of-Interest Analyses

We performed regions-of-interest (ROIs) analysis as a follow-up of the whole-brain analysis to relate brain responses in the semantic categorization task. ROIs were prior selected based on regions that were reported as fundamental to semantic naming of categories in a sample of Western young subjects (Chouinard, & Goodale, 2010). These ROIs were: left inferior temporal gyrus (left ITG, coordinate in Talairach space: x, y, z = -48, -46, -16), left parahippocampal gyrus (left PHG, coordinate in Talairach space: x, y, z = -34, -30, -16), and left inferior frontal gyrus (left IFG, coordinate in Talairach space: x,

y, z = -42, 22, 6). In addition, we are aware that older adults typically display a more bilateral pattern of functional activation than young adults (Dennis & Cabeza, 2008; Grady, 2008; Park & Reuter-Lorenz, 2009), we thus selected the ROIs located in the homologous site of the right hemisphere that mirrors the center of coordinate in Chouinard & Goodale (2010), yielding three ROIs in right hemisphere of the brain: right IFG (coordinate in Talairach space: x, y, z = 48, -46, -16), right PHG (coordinate in Talairach space: x, y, z = 34, -30, -16), and right IFG (coordinate in Talairach space: x, y, z = 42, 22, 6). Estimates of the responses to semantic categorization relative to control condition (semantic categorization > control contrast) were then extracted from these six ROIs within 6 mm radius around the center of coordinate for each participant using Marsbar software (Brett et al. 2002).

fMRI: Laterality Analyses

We next looked for evidence of the effect of culture on age-related laterality difference. A laterality analysis was performed to systematically assess the laterality of functional activation over the common brain regions that showed significant task-positive effect (i.e. semantic categorization > control condition) across age and culture group in the whole-brain analysis. These ROIs were then identified in automated anatomical labeling (AAL, Tzourio-Mazoyer, et al., 2002) provided with SPM software to yield masks that used for laterality analysis.

Laterality indices were based on the standard formula (Everts, et al., 2009):

Laterality = [(Σvoxel left –Σvoxel right)/(Σvoxel left +Σvoxel right)]

This formula results in positive values for predominantly left-lateralized activity

(laterality > 0.1), negative values for predominantly right-lateralized activity (laterality < -0.1), and values between 0.1 and -0.1 for bilateral activity (Everts et al., 2009; Powell et al., 2012). To ensure the findings laterality differences in these regions were not due to the significance threshold selected for analyzing fMRI data, we computed laterality indices using boostraping approach (Wilke & Schmithorst, 2006).

Results

Behavioral Results

Table 8 shows the results of accuracy and RTs during the semantic categorization task for each group.

Results from a culture x age ANOVA for accuracy revealed an interaction between cultural group and age [$F(1,177) = 6.20$, $p < .05$], with lower accuracy for older Singaporeans compared to other groups. There was no significant effect of age [$F(1, 177) = 3.215$, $p = 0.08$], or cultural group [$F(1, 177) = 0.75$, $p = 0.39$].

Results from another 2 x 2 ANOVA for RTs revealed a main effect of age [$F(1,177) = 35.66$, $p < .01$], with slower RT for older adults than young adults. The interaction between age and cultural group was significant [$F(1,177) = 11.06$, $p < .01$], with a greater age-related slowing response for Singaporeans than Americans. There was no significant effect of cultural groups on RTs [$F(1,177) = 2.09$, $p = 0.15$].

Neuropsychological Assessment and Schwartz Value Survey

The results of neuropsychological testing and Schwartz Value Survey were described in Chee et al. (2010). Analyses of neuropsychological tests revealed a main effect of age

for each cognitive task, with older adults showing slower RTs, declined working memory and mental control performance. In addition, there was an age x group interaction on the WAIS-R Digit-Symbol task, with Singaporeans showing greater effect of age (older adults were worse than young adults) compared to Americans. These results suggest that aging systematically associated with significantly declines in cognitive performance (Park, et al., 2002).

Analyses of the subscales from the Schwartz Value Survey showed the expected cultural biases, with Singaporean showing higher collectivistic values than Americans. There were also main effects of age on almost every subscale of Schwartz Value Survey, with older adults endorsing more collectivistic values and young adults endorsing greater individualistic values. These data indicates that the groups held to values commonly associated with their respective cultures.

fMRI Results: Whole Brain Analyses

Figure 11 shows the results of whole brain analysis of common brain responses to the semantic categorization vs. control conditions across groups (with masking out brain regions showing task by culture interactions) and Table 9 lists the peak location of this analysis. Young and older Singaporeans and Americans revealed activity in bilateral inferior frontal regions, left precentral region, left posterior parietal regions, supplementary motor area (SMA), bilateral inferior occipital regions, parahippocampus and hippocampus, reflecting a culture-invariant neural network associated with retrieving and manipulating semantic representations during semantic categorization.

fMRI Results: ROI Analyses

We next examined the BOLD-measured neural responses during the semantic categorization relative to control conditions in the ROIs that are fundamental to semantic naming of categories reported in previous study (Chouinard, & Goodale, 2010) and those in the homologous site of the right hemisphere. Figure 12 shows the extracted responses from each ROI.

The Effect of Culture

The Culture x Age ANOVA yielded a significant effect of culture on the left inferior frontal gyrus [$F(1, 187) = 7.13$, $p< 0.01$], with American showing greater activation than Singaporeans. Interestingly, the effect of culture on the right inferior frontal gyrus was significant [$F(1, 187) = 4.38$, $p< 0.05$], with Singaporeans showing greater activation than Americans. We did not find any effect of culture in other ROIs (left inferior temporal gyrus: $F(1, 187) = 0.12$, $p=0.55$; right inferior temporal gyrus: $F(1, 187) = 0.12$, $p=0.55$; left parahippocampal gyrus: $F(1, 187) = 1.46$, $p=0.23$; Right parahippocampal gyrus: $F(1, 187) = 0.03$, $p=0.87$). These results suggest that there is a qualitative difference between cultural groups in neural networks used to perform semantic categorization task, particular in prefrontal regions.

The Effect of Age

The effect of age was also observed on semantic network isolated from meta-analysis study. We found that older adults showed greater activation in inferior frontal gyrus (left: [$F(1, 187) = 17.39$, $p< 0.01$]; right: [$F(1, 187) = 37.88$, $p< 0.01$]) compared to young adults, consistent with many previous findings (Dennis & Cabeza,

2008; Grady, 2008; Park & Reuter-Lorenz, 2009). Young adults, however, elicited greater activation in the left parahippocampus ($[F(1, 187) = 4.21, p < 0.05]$) and inferior temporal gyrus ($[F(1, 187) = 6.03, p < 0.05]$) but not in right hemisphere compared to older adults. Consistent with the literature in cognitive neuroscience of aging, such age-related pattern of decreased activity in posterior region of the aging brain coupling with increased activity in frontal cortex has been reported as a Posterior Anterior Shift in Aging (PASA) functional activation (Davis et al., 2008; Goh et al., 2010).

The interaction of Culture and Age

Finally, we did not find any culture x age interaction in this ROI analysis (left inferior frontal gyrus: $F(1, 187) = 0.45, p = 0.51$; right inferior frontal gyrus: $F(1, 187) = 0.29, p = 0.59$); left parahippocampal gyrus: $F(1, 187) = 0.34, p = 0.56$; Right parahippocampal gyrus: $F(1, 187) = 0.27, p = 0.61$; left inferior temporal gyrus: $F(1, 187) = 0.36, p = 0.55$; right inferior temporal gyrus: $F(1, 187) = 0.04, p = 0.95$).

fMRI Results: Laterality Analysis

We next looked for evidence of the effects of culture and age on difference in laterality of functional activation. Figure 13 shows the laterality of functional activation over each ROI for each group. Laterality analyses were performed to systematically assess the laterality of functional activation over the common brain regions that showed significant task-positive effect (i.e. semantic categorization > control condition) across age and culture group in the whole-brain analysis. These selected brain regions were: precrntral gyrus, inferior frontal gyrus, middle frontal region, inferior parietal lobule, superior parietal lobule, inferior temporal region, inferior occipital region, and

hippocampus (see Table 9 for corresponding coordinate in MNI space).

The Effect of Culture

The culture x age ANOVA on laterality index yielded significant effects of culture on inferior frontal gyrus [$F(1, 160) = 4.87$, $p < 0.05$], inferior temporal region [$F(1, 177) = 17.54$, $p < 0.01$], and inferior occipital region [$F(1, 187) = 5.42$, $p < 0.05$]. Specifically, Singaporeans showed more bilateral activation in inferior frontal gyrus and inferior temporal region compared to Americans, whereas American displayed more bilateral activation in inferior occipital region compared to Singaporeans (Fig. 13). There was no significant cultural difference on laterality of activation on middle frontal gyrus [$F(1, 165) = 0.64$, $p = 0.43$], precentral gyrus [$F(1, 164) = 3.76$, $p = 0.06$], inferior parietal lobule [$F(1, 122) = 1.63$, $p = 0.20$], superior parietal lobule [$F(1, 163) = 2.71$, $p = 0.10$], and hippocampus [$F(1, 100) = 0.06$, $p = 0.81$].

The Effect of Age

The 2 x 2 ANOVA on laterality index also yielded significant effects of age on every selected brain region (precentral gyrus: $F(1, 164) = 25.08$, $p < 0.01$; inferior frontal gyrus: $F(1, 160) = 25.22$, $p < 0.01$; middle frontal gyrus: $F(1, 165) = 17.76$, $p < 0.01$; inferior parietal lobule: $F(1, 122) = 4.78$, $p < 0.05$; superior parietal lobule: $F(1, 163) = 16.32$, $p < 0.01$; inferior temporal region: $F(1, 177) = 29.09$, $p < 0.01$; inferior occipital region: $F(1, 187) = 7.42$, $p < 0.01$; marginally significant on hippocampus: $F(1, 100) = 3.25$, $p = 0.074$). Older adults elicited more bilateral pattern of functional activation from anterior to posterior regions of the aging brain compared to young adults (Fig. 13). Consistent with the literature in cognitive neuroscience of aging, such global nature of age-related

bilateral activation has been identified as the pattern of Hemispheric Asymmetry

Reduction in OLDer adults (HAROLD; Cabeza, 2002).

The interaction of Culture and Age

Finally, we did not find any culture x age interaction in this laterality analysis on the

ROIs (precentral gyrus: $F(1, 164) = 1.02$, p=0.31; inferior frontal gyrus: $F(1, 160) = 0.37$,

p = 0.55; middle frontal gyrus: $F(1, 165) = 5.84$, p< 0.05; inferior parietal lobule: $F(1,$

$122) = 0.76$, p=0.39; superior parietal lobule: $F(1, 163) = 1.34$, p=0.25; inferior temporal

region: $F(1, 177) = 1.47$, p=0.23; inferior occipital region: $F(1, 187) = 2.97$, p=0.08;

hippocampus: $F(1, 100) = 0.12$, p = 0.73)

Discussion

We provide evidence that culture-related differences in cortical recruitment may

remain throughout the lifespan, and age-related changes in cortical recruitment appear to

be ubiquitous across individuals with different experiential background. Although in

older adult individuals who show greater susceptibility to neurobiological decline with

aging and thus poorer cognition, the effect of age do not completely diminish individual

differences in brain functional activation that arise from external experience, at least

those associated with cultural bias. In addition, the effect of age was characterized by

displaying a global influence on brain function, with a more bilateral pattern of neural

activation (i.e., Hemispheric Asymmetry Reduction in OLDer adults, HAROLD; Cabeza,

2002) and an greater anterior-to-posterior gradient distribution of reduced functional

activation (Posterior Anterior Shift in Aging, PASA; Davis et al., 2008) for older adults

compared to young adults. The effect of culture, however, appears to be more localized on brain function, with more bilateral activation in prefrontal and temporal subregions for East Asians compared to Westerners, suggesting that experience-dependent functional modulations are more specific (Park et al. 1999; Goh et al. 2007).

This cross-cultural comparison of young and older adults illustrated that while age-related recruitment in neural correlates corresponding to semantic processes were manifested cross-culturally in older adults, culture-related neural differences, once attained, may continuously shape functional activation across the lifespan (Park & Gutchess, 2002, 2006). Moreover, the effect of culture was found in specific regions in frontal and temporal cortex. These data illustrate the importance of culture in shaping neural functioning, but they also demonstrate the plasticity of the aging brain and moreover, the fact that the influence of cultural experience on the neural plasticity may be in a manner of specific processing biases. The similar idea has been proposed in previous neuroimaing studies when other types of external experience such as training and aerobic exercise were conducted on young and older adults. For example, Draganski et al. (2004) demonstrated that a short period of training in juggling by inexperienced young adult displayed increased brain volume than non-jugglers in the bilateral midtemporal area and left posterior intraparietal sulcus, the brain regions that are associated with processing of visual motion. Following that, Boyke et al. (2008) applied the same procedure to older adults and reported a similar increase of brain volume in old adults in the mid-temporal region with their young jugglers. This structural imaging finding and our functional MRI results thus provide clear evidence for experience-based plasticity in both young and older adults, with specific and localized effect on the brain region that processing are

associated with.

Although we did not observe that older adults became more acculturated than young adults in this study, that would thus indicate that external experience might subvert age-related changes, we note that cultural biases acquired through cultural experience were maintained in the older adults and did not converge, suggesting that the effect of age did not overwhelm the effect of experience. However, Goh et al. (2007) using functional MRI-Adaptation (fMR-A) approach[1] reported a divergent interaction between age and culture when East Asian and Western young and older participants viewing quartets of pictures. They found that older adults displayed more cultural differences than young adults, under circumstances in which attentional resources were more limited. Therefore, it is possible that the reasons we did not find age x culture interaction in neural activation as Goh et al. (2007) did are because the semantic categorization task we used in this study is a relatively easy task for older adults, and two studies utilized different neuroimaging approaches. In addition, the different findings between two cross-cultural aging neuroimaging studies could reflect differential effect of aging on prefrontal and ventral visual cortex (Goh et al. 2010).

We reported more bilateral patterns of functional activation in inferior frontal gyrus and inferior temporal region for East Asians. There is evidence that left inferior frontal gyrus is highly associated with semantic processing (Bookheimer, 2002) and inferior temporal gyrus is specialized for processing the identity of letters and words (Polk et al. 2002). The observed cultural differences in these two regions, as suggested by Gutchess

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[1] The fMRI adaptation paradigm allows for the evaluation of neural selectivity and specialization based on the phenomenon that neural response to repeated stimuli is typically reduced (Grill-Spector & Malach, 2001).

et al. (2010), may reflect a greater effort for East Asians in retrieving semantic

information and processing the identity of letters/words when performing

culturally-non-preferred semantic judgment using verbal stimuli. Moreover, we reported a

culture-related difference in occipital regions, with more bilateral pattern of functional

activation in this area for Westerners (or more left-lateralized activation for East Asians).

There is evidence that occipital regions are part of ventral visual pathway and appear to

be specialized to recognize objects (Grill-Spector et al., 1998; Malach et al., 1995). The

greater involvement of this region for Westerners may reflect that they are more analytic

about the features of the living/non-living items, attending more to spatial properties of

the items than do East Asian, in keeping with a greater focus on analytic/categorical

rather than holistic/functional cognitive style for Westerners (Goh & Park, 2009;

Kitayama & Uskul, 2011; Masuda & Nisbett, 2001; Nisbett & Masuda, 2003).

In contrast to the more global effect of aging, the present study demonstrated that

cultural differences in neural function are consistently associated with the

categorical-functional dichotomy of processing style in Westerners and East Asians

respectively. However, we also found age x culture interaction on one of

neuropsychological data - the WAIS-R Digit-Symbol task, with Singaporeans showing

greater effect of age (older adults were worse than young adults) compared to Americans.

Such culture differences in digit-based measures may derive from the fact that Chinese is

less syllabically dense than English and permits more efficient rehearsal (Cheung &

Kemper, 1993, 1994). Along this line, Hedden et al. (2002) assessed processing speed

between a sample of old and young adults tested in China and the United States. They

reported that when numerically based tests of processing speed were used (e.g., digit

comparison), older Chinese showed worse performance compared to old Americans. In contrast, when more neutral, spatial based tasks were used (e.g., pattern comparison) the processing speed for young and old participants were equivalent. They suggested that such group differences could be due to differences in the number system and representation in the Chinese and English languages, rather than actual cognitive differences in speed processing. Thus, our result of cultural variations in number-based processing speed is consistent with previous findings in cultural literatures and reflects a bias in measures rather than cultural differences in cognition, Future studies should be aware of such differences in the stimuli used to ensure comparability of cognitive processing across cultural and age groups.

Although the performance in accuracy is equivalent between age group and between cultural groups, we found culture x age interactions on accuracy and reaction times when semantic categorical task were performed, with lower accuracy and slower reaction times for older Singaporeans compared to other groups. We speculate that these results may reflect cohort-related effects within a cultural group. Despite English is the official language in Singapore, English is likely a second language for old Singaporeans due to socio-historical changes and thus, slower response times and less accuracy may occur for older Singaporeans to recognize English words in order to access to correct categorical information and semantic knowledge embedded in the presented words.

In conclusion, while age-related bilateral recruitment of neural activation in response to semantic categorization was evident across older adults from both cultural groups in cerebral cortex, the effect of cultures on neural activation were only seen in the inferior frontal, inferior temporal, and occipital regions. Moreover, the direction of cultural

differences depends on the region with East Asian showing more bilateral inferior frontal and inferior temporal activation and Westerners showing more bilateral occipital activation, in line with functional and categorical processing style, respectively. Our results are also consistent with a more bilateral pattern of neural activation as a fundamental biological effect in aging that extends across individuals from different cultural backgrounds. This age effect did not interact with the more localized and specific cultural effects, indicating that age did not serve to accentuate or diminish cultural differences in this sample.

Tables

Table 8. Accuracy (standard deviation) and response times during semantic categorization task for young and older Americans (US) and Singaporeans (SG).

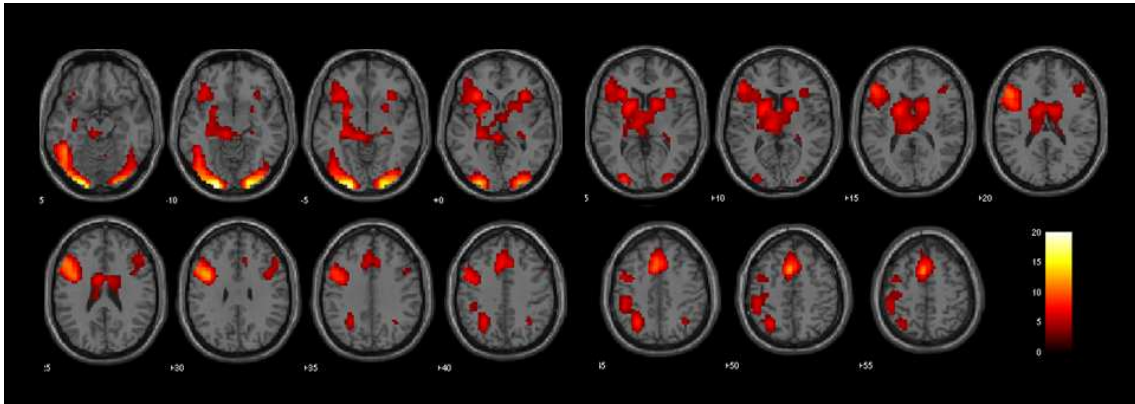|	US		SG	
	Young	Older	Young	Older
Accuracy (%)	98.7 (2.7)	99.0 (2.3)	99.3 (1.6)	97.8 (2.5)
Response Time (ms)	1033.5 (193.1)	1099.9 (140.0)	985.3 (128.3)	1219.5 (182.3)

Figures

Figure 11. Common brain regions across age and cultures. Conjunction analysis show brain regions exhibiting greater activity (Semantic Judgment vs. Control conditions) across age and culture groups (≥10 contiguous voxels with p < 0.001, uncorrected).
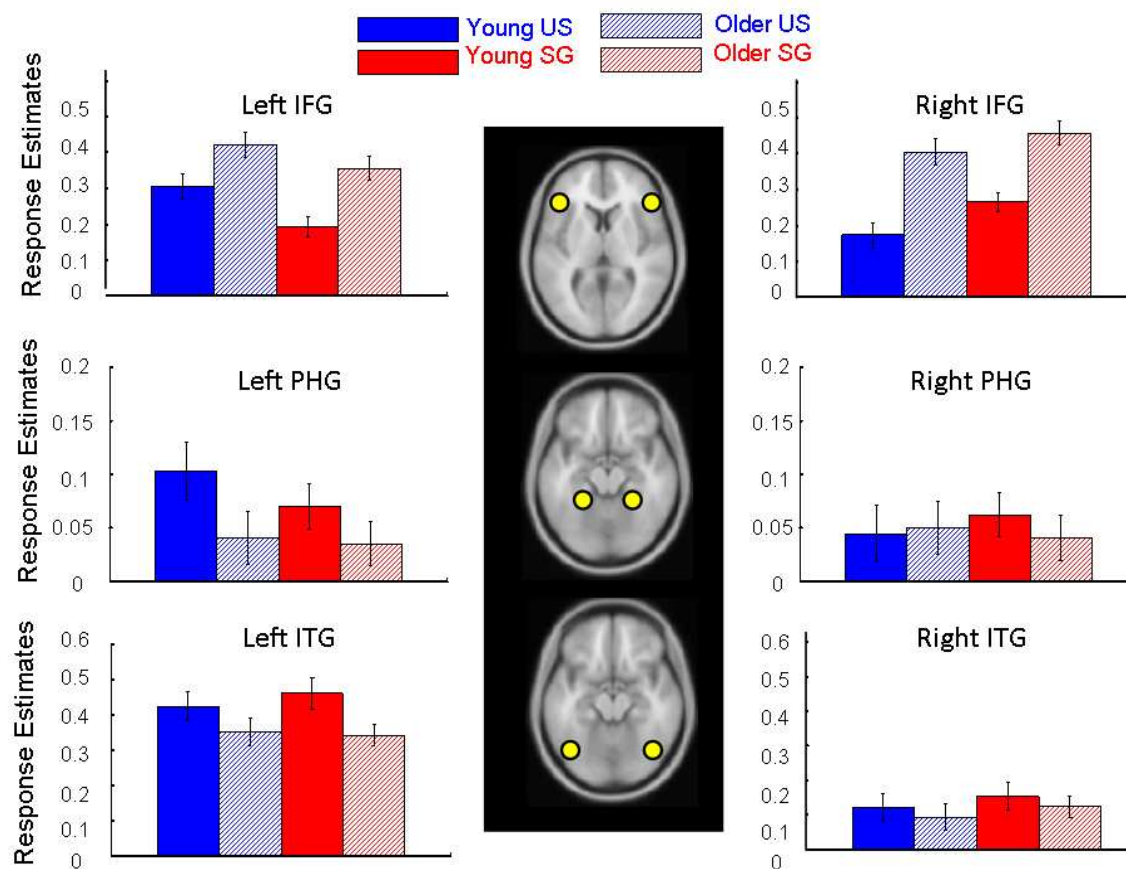
Figure 12. BOLD-measured responses during semantic categorization relative to control conditions in the regions isolated on meta-analysis to be semantic judgment areas (Chouinard, & Goodale, 2010). Error bars show standard errors. IFG, inferior frontal gyrus; PHG, parahippocampal gyrus; ITG, inferior temporal gyrus.
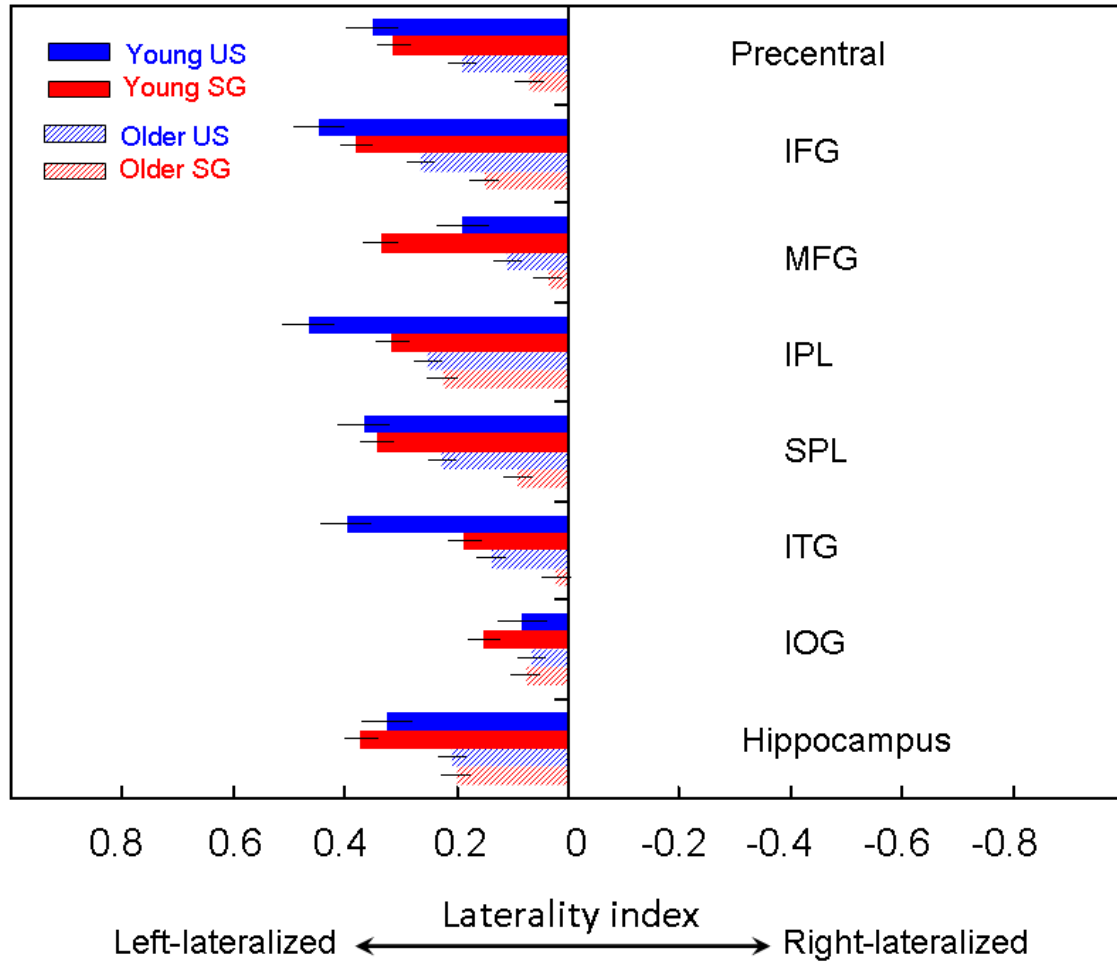
Figure 13. Group differences in laterality. The threshold-weighted mean values indicate laterality of functional activation during semantic categorization task over precentral gyrus, inferior frontal gyrus (IFG), middle frontal gyrus (MFG), inferior parietal lobule (IPL), superior parietal lobule (SPL), inferior temporal gyrus (ITG), inferior occipital gyrus (IOG), and hippocampus in young and older Singaporeans and Americans. Laterality are computed according to: $[(\sum voxel_{left} - \sum voxel_{right})/(\sum voxel_{left} + \sum voxel_{right})]$, with laterality >0.1 for left-lateralized activation, laterality < -0.1 for right-lateralized activation, and values between 0.1 and -0.1 for bilateral activity.

CHAPTER 5

GENERAL DISCUSSION

In summary, this series of studies, including fMRI and DTI measures, provide the missing links that demonstrate (1) different patterns of age-related changes in cortical recruitment stem from a reduced capacity that limits older adult's ability to recruit more neural activity in response to increasing task demands, (2) the source of the age-related changes in cortical recruitment may be traced to individual differences in white matter integrity of corpus callosum, and (3) these age-related differences in bilateral cortical recruitment may be selectively modulated by culture-related experiences. Three experiments were performed to arrive at these conclusions.

Experiment 1 provides evidence that while younger adults demonstrated an increase in the activation of cortical regions responsible for cognitive control with increasing task demands, older adults failed to modulate BOLD-measured activity under higher levels of task demand, indicating reduced or limited capacities of recruiting more neural resources in response to increasing task demands with age. Experiment 2 provides further evidence that individuals with greater micro-structural integrity of white matter, particular in corpus callosum, were related to more bilateral cortical recruitment (indexed as laterality index) and better task performance (indexed as interference percentage), indicating a critical role of corpus callosum for recruiting additional neural resources between two hemispheres in response to changing task demands across the lifespan. Moreover, older adults showed greater integrity of posterior corpus callosum were related to better performance but this association was not observed in young adults. Finally, Experiment 3

provides evidence that age-related changes in cortical recruitment appear to be ubiquitous across individuals with different experiential background. Whereas the effect of age was characterized by displaying a global influence on brain function, with older adults showing greater bilateral activation as well as reduced anterior-to-posterior activation than young adults, the effect of culture appears to be more localized on brain function, with East Asians showing more bilateral activation in prefrontal and temporal subregions than Westerners. The data suggests differential influences of aging and culture on functional brain changes, with more global effect for biological aging and more localized effect for culture-related experience.

Concerns have been raised that, when comparing BOLD fMRI data from different groups , particular between younger and older adults, the functional effects may be confounded by changes in neurovascular coupling (D'Esposito et al., 1999, 2003; Huettel et al., 2001). Moreover, individual differences in bodily systems, including the cardiovascular and cardiopulmonary systems, may have both direct and indirect effects on neural activity (Lu et al., 2011; Raz et al., 2008). Therefore, it is possible that the CRUNCH pattern we observed in previous fMRI studies and current studies could be partially due to age-related reduced capacity in neurovascular system and dysfunction of cardiovascular system. Such effects may result in the limitation of recruiting additional oxygenated blood of the aging brain and/or the earlier ceiling effect on BOLD-related signal in older adults. Some methodological approaches disentangle these problems and rule out these potential confounds. First, we could record both neuronal and hemodynamic measures concurrently by conducting different but complementary neuroimaging techniques together, including measures of neuronal function such as

event-related optical signal (EROS; Fabiani & Gratton, 2005), measures of hemodynamic function such as functional near-infrared spectroscopy (fNIRS; Villringer & Chance, 1997), measures of electrophysiological signal such as event-related potential (ERP, Fabiani, Gratton, & Federmeier, 2007) in addition to fMRI tool. Second, we could calibrate BOLD fMRI data with a means of hypercapnia using simple breath-holding paradigm during functional MRI session (Thomason et al., 2007). This approach has been suggested to sufficiently reduce vascular variability in different groups such as children (Thomason et al., 2005) and older adults (Handwerker et al., 2007).

Resolving whether age-related over-recruitment is associated with compensatory or declining function, would require studies that more effectively measure and equate differences in cognitive ability and performance across young and older adults, as well as better define what compensation means. In the present fMRI studies, compensatory process refers to brain activity that results in an optimal behavioral performance in accuracy and reaction times as opposed to some other definitions that do not necessarily require a behavioral index. Older adults showed equivalent accuracy but generally slow responses during lower levels of task demands coupling with successful modulation of BOLD-measured activity (older adults for Experiment 1 and Western older adults for Experiment 3). In addition, older adults showed equivalent accuracy but a trend of slower reaction time during higher levels of task demands coupling with a failure of modulation of BOLD-measured activity (older adults for Experiment 1). These fMRI results appear to support the compensatory view. Further, DTI study in Experiment 2 provides evidence from individual's anatomical information of white matter integrity that seems also supports compensatory view, with greater integrity of callosal fibers associating with

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better performance and more bilateral activation.

It is worth pointing that we performed a systematical assessment in the laterality of functional activation between age groups and between cultural groups across three experiments. This assessment allow us to ensure the findings of age-related and/or group-related laterality differences in specific brain regions are not due to the significance threshold selected for analyzing fMRI data. It has been suggested that, based on the statistical characteristics of fMRI data, different thresholds could mislead the observed fMRI results and further incorrectly interpret the effect of age and the effect of condition (Cabeza 2002). Therefore, in addition to the classical approaches, including a measure of strength of functional activation such as BOLD signal changes and a measure of spread of functional activation such as voxel counting, we computed laterality indices for each individual (Wilke & Schmithorst 2006). The approach based on threshold-dependent laterality curves and on bootstrap analysis, that is, based on a variety of different activation thresholds and then computed a weighted average of the laterality indices, giving more weight to indices that were computed using higher thresholds. This approach provides a more reliable and more systematic assessment to observe hemispheric asymmetry of functional activation between different groups.

In conclusion, this series of studies provide the missing links that demonstrate that different patterns of age-related changes in cortical recruitment stem from a reduced capacity to recruit neural resources for older adults in response to increasing task demand, and such differences in cortical recruitment could be related to individual differences in integrity of corpus callosum and could be selectively modulated by culture-related external experiences.

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