FUNCTIONAL COMPENSATION IN RESPONSE TO INCREASING TASK
DIFFICULTY: COMPARING SEMANTIC AND EPISODIC MEMORY TASKS IN
YOUNG AND OLDER ADULTS

by

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A Dissertation Submitted to the Faculty of the

DEPARTMENT OF PSYCHOLOGY

In Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

THE UNIVERSITY OF ARIZONA

2017

THE UNIVERSITY OF ARIZONA
GRADUATE COLLEGE

As members of the Dissertation Committee, we certify that we have read the dissertation

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ACKNOWLEDGEMENTS

DEDICATION

To my parents, Dr. Edgardo Baena and Ana Myriam Rivero de Baena: "con los pies en la tierra y las ilusiones enganchadas a una estrella".

To my siblings, Dr. Antonio Luis Baena Rivero, Dr. Carol Lilian Rodriguez, Dr. Johanna Baena-Rivero and Dr. Juan Manuel Adames.

To my little kids, Jeronimo Antonio, Sebastian Antonio and Josephine Olga.

To the rest of my family, but in particular to my grandfathers: Dr. Antonio Baena Sayas, and Dr. Armando Rivero. And my amazing three grandmothers: Josefina Pianeta de Baena, Myriam Florez de Rivero, and my lela, Olga Cecilia Rivera.

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ABSTRACT

Previous fMRI studies have demonstrated that older adults who perform as well as young adults on certain cognitive tasks recruit additional brain regions relative to younger adults while performing these tasks. This phenomenon has been interpreted as a compensatory response and may reflect an effort to maintain performance in the face of increasing changes in cognitive difficulty or age-related brain changes in structure and/or function. Whether the compensatory response is specific to older adults or represents a more general response of any individual to increasing task difficulty is unclear. The present fMRI experiment explored age differences in brain activity associated with increases in task difficulty in two tasks, an episodic-retrieval task that is expected to be difficult for older compared to young adults, and a lexical-semantic task that is expected to be more difficult for young compared to older adults. In the lexical-semantic task, participants judged whether pairs of words were synonyms or antonyms. In the episodic task that followed, participants made yes/no memory judgments for the word pairs previously presented. Difficulty was manipulated using word frequency -low frequency words are more difficult in the lexical-semantic judgment task and easier in the episodic task. Young (ages 18-24) and older healthy adults (ages 60-83) were scanned on a 3T GE magnet using a single-shot spiral pulse sequence. Behavioral results showed a double dissociation – older adults were adversely affected by word frequency in the episodic but not the semantic task, while young adults were adversely affected by word frequency in the semantic but not the episodic task. Both groups showed activation in similar task-related and task-general regions regardless of difficulty level). Age-related differences were observed for *task-specific* and linear increases due to difficulty. Linear increases in fMRI activation were associated with younger adults showing increased task difficulty in bilateral task-related regions during the lexical semantic task, whereas in the episodic retrieval task only activating bilateral posterior cortices. As difficulty increased, older adults showed unilateral brain activations: left regions for the lexical-semantic task and medial and right hemisphere regions for the episodic retrieval task. Most importantly, difficulty load increases paralleled the groups' behavioral results: younger adults showed greater increases in activity in the lexical-semantic task compared to older adults, but not in the episodic retrieval task, whereas older adults showed the opposite pattern, with greater increases in activation only in the episodic task when compared to younger adults. Thus, younger and older adults recruit regions differently in response to increases in difficulty. Our results suggest that increases in fMRI activation as difficulty increases occur as an interaction to deal with task difficulty and the inherent abilities of the individuals, rather than occurring only in older adults, or in older adults across all tasks, regardless of their abilities in that domain.

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CHAPTER 1:

INTRODUCTION

In a world where the older adult population can be expected to increase

substantially over the next several decades (UN, 2009), it is increasingly important to

advance research on how aging affects cognitive function (Alexander et al., 2012). Large

individual differences in cognitive function exist among older adults, extending from a

subset of older adults who maintain high levels of function throughout their lifespan to

others who show signs of pathological aging and clinical dementia (Daffner, 2010, see

also Buckner, 2004; Hedden & Gabrieli, 2004). Regardless of whether older adults show

pathological aging or healthy age-related changes in cognitive function, the most

common and consistent complaint among the elderly is memory difficulties. The degree

of such memory deficits varies among the elderly and not all types of memory are equally

affected (see Hultsch et al., 1999; Park et al, 2002, Rönnlund, Nyberg, Bäckman, &

Nilsson, 2005). Data from research that investigates patterns of decline and stability in

memory across human adulthood suggest that as individuals age, working memory

(maintenance, monitoring, and manipulation of information over a short delay) and

episodic memory (memory for personally experienced past events) generally decline in

older adults, while semantic memory (memory that represents our accumulated

knowledge of the world, including facts and vocabulary) remains stable or even improves

across the adult lifespan (for review, see Hedden & Gabrieli, 2004).

Despite well-established age-related declines and preserved cognitive abilities,

there are substantial individual differences in cognitive function between older adults and

within cognitive domains. Longitudinal studies investigating changes in cognitive

functions suggest that a variety of episodic memory tasks (free recall, source memory),

along with working memory (maintenance, monitoring, and manipulation of information over a short delay), speed of processing, inhibitory functions, and executive functions (e.g., monitoring and attentional processes, inhibition, task-switching, planning ability) are the cognitive domains most affected by age (for reviews, see Hedden & Gabrieli, 2004; Park & Schwarz, 2000; Nilsson et al., 2002; Rönnlund at el., 2005). For example, Park et al. (2002), in their cross-sectional study, tested adults ranging in age from 20-89 on measures of speed of processing, working memory, long-term memory (a measure of episodic memory), and world knowledge (a measure of semantic memory). The results showed no age-related declines in world knowledge as compared to the other measures. In addition, Hultsch et al. (1999), using data from the Victoria Longitudinal Study, showed greater age-related declines in speed of processing, working memory, and list recall (a measure of episodic memory) compared to vocabulary (a measure of semantic knowledge), although the size of the age-related decline was considerably smaller than the cross-sectional results reported by Park et al. (2002). Such results have led to the conclusion that aging may be associated with deficits in episodic memory and working memory, whereas semantic knowledge, including world knowledge and vocabulary, shows no or little decrement.

Additional evidence highlighting similar findings comparing both longitudinal and cross-sectional data showed large individual differences among older adults in the degree to which they experience declines in episodic memory, whereas semantic memory tasks showed few or no decrements (Rönnlund at el., 2005). Semantic tasks that decline with age are generally those that require rapid retrieval of information, such as category fluency, suggesting problems with efficient retrieval rather than a deficit in semantic

knowledge or representations (Nyberg et al., 2003).

The large individual variability in age-related memory deficits may be mediated by changes in the medial temporal lobe (MTL) and the frontal lobe (FL), primarily in the prefrontal cortex (PFC), which are engaged differently but interactively during memory tasks. For example, Glisky, Polster and Routhieaux (1995) administered a battery of neuropsychological tests to older adults who then completed a source memory test and an item memory test. The scores from the neuropsychological tests were entered into a factor analysis that produced two composite scores (i.e., factor scores): memory and executive function. It is important to note that the memory and executive function factors are assumed to represent underlying MTL and FL functions, respectively. The factors were validated in two subsequent studies, one with 100 participants (Glisky, Rubin & Davidson, 2001) and the other with a normative sample of 227 older adults (Glisky & Kong, 2008). Glisky et al. (1995) demonstrated a double dissociation: participants with low executive function scores were impaired in source memory but not in item memory, whereas those with low memory function scores were impaired in item memory but not in source memory. Furthermore, Glisky et al. (2001) showed that older adults with poor executive functions present with a source memory deficit, but that deficit improved when the study task directed their attention to integrating contextual information with the item information during encoding. These results provide additional support to claims that executive functions contribute to some types of memory performance but not others, and that the variability in observed age-related changes in memory may be due to changes in function of the frontal lobes or the medial temporal lobes.

Evidence of age-related morphological changes in the brain that parallel declines

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in cognitive functions across the lifespan offer an explanation for the large individual differences observed in older adults, supported by the results from various imaging studies. Structural neuroimaging studies have shown preferential decrease in gray matter volume in frontal regions, as well as in areas in the parietal and temporal cortex (Alexander et al., 2006; Bergfield et al., 2010). Additionally, morphological changes in frontal cortex correlate most consistently with declines in cognitive function and subsequently to age-related declines (Dempster, 1992; West, 1996). For example, morphometric analyses of structural MRIs suggest that gray matter in the frontal lobes shows preferential declines with age (Raz, 2000), with significant reductions in gray matter volume in frontal lobe regions over a 5-year period (Raz et al., 2005). The reduction in frontal lobe volume, primarily in the PFC, is one of the most consistently hypothesized mediators of the age-related effects observed in episodic memory and executive functions (Dempster, 1992; West, 1996). In contrast, MTL structures show smaller volumetric age-related reductions than those in the prefrontal cortex (Raz, 2000; Raz, 2005), and these reductions are more variable across individuals and across multiple studies (Raz, 2000). Age-related hippocampal atrophy has also been associated with reductions in episodic memory performance in older adults (Raz, Gunning-Dixon, Head, Dupis & Acker, 1998), although there is conflicting evidence (for review, see Van Petten, 2004).

A separate factor, which has also been hypothesized to be contributing to cognitive decline in older adults is white matter deterioration, which is related to gray matter regional atrophy (Raz et al., 2005). For example, Raz et al. (2005) reported a correlation between hippocampal volume and the volume of abnormal white matter in

the frontal lobes of older adults. Head et al. (2004) showed that the greatest declines in white matter structural integrity, as measured by diffusion MRI, were observed in the anterior regions of the brain, suggesting that frontal lobe white matter may be more vulnerable to aging relative to white matter in posterior regions (See also Davis et al., 2008; Davis et al., 2009; Madden et al., 2007; Pfefferbaum et al., 2000; Salat et al., 2004), although these results are not always consistent across studies (Ryan et al., 2011).

Furthermore, while structural neuroimaging measures characterize age-related structural changes, results from functional MRI studies provide support for the view that functional changes in the PFC (Raz, 2005) and possibly in MTL (see Park & Gutchess, 2005) also contribute to declines in cognitive functions among older adults. These age-related changes are especially prominent in the frontal cortex and sometimes evident in medial temporal areas. Since white matter tracts facilitate communication among brain regions, these changes may be especially important for understanding age-related cognitive changes and individual differences among cognitive domains.

In fMRI studies, differences have been reported in the blood-oxygen-level-dependent (BOLD) signal in older as compared to younger adults. For example, Grady et al (1995) reported reduced PFC activation during encoding and recognition in older adults when compared to younger adults (see also Rypma & D'Esposito 2000, Logan, Sanders, Snyder, Morris, & Buckner, 2002; Park et al., 2004; Colcombe, Kramer, Erickson, & Scalf, 2005; Persson et al., 2006; Carp, Park, Polk, & Park, 2011). On the other hand, several studies have found significantly increased bilateral PFC activity in older adults compared to young adults while performing a variety of tasks (Grady et al., 1994; Cabeza, 1997; 2002; Cabeza et al., 2002; Rosen et al., 2002; Morcom, Good,

Frackowiak & Rugg, 2003; Maguire & Frith, 2003; Persson et al., 2004; Wierenga et al, 2008; Bergerbest et al., 2009; Tyler et al., 2010; Sala-Llonch et al., 2012).

It has been suggested that these conflicting results could reflect the following possible mechanisms:

First, over-recruitment has been interpreted as less efficient use of neural resources or dysfunction and/or *dedifferentiation* without any behavioral benefit (Lindenberger et al., 2001; St-Laurent et al., 2014; Park et al., 2004; Voss et al., 2008; Carp et al., 2011; Bernard & Seidler, 2012; Burianová et al., 2013). Second, increases in brain activity have been interpreted as a *compensatory response* when additional recruitment of resources are associated with better performance in older adults or at least equal behavioral performance within older and younger adults (Cabeza, 2002; Reuter-Lorenz & Lusting, 2005; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park 2010; for a review see Grady, 2012).

Finally, it has been recently suggested that dedifferentiation may occur simultaneously with or as a mutual consequence of the compensatory response without a successful behavioral association or as a *failed compensation attempt* just as a functional age-related reorganization (Cabeza & Dennis, 2013; see Dennis & Cabeza, 2011; Spaniol & Grady, 2012; Burianová et al., 2013; Hakun et al., 2015; Vermeij et al., 2014).

Compensation: Theoretical views.

In the past two decades, neuroimaging studies have shown that older adults tend to engage bilateral frontal regions to a greater degree than young adults, a phenomenon usually described as a compensatory response that pairs increased brain recruitment with

behavioral performance at the same level as young adults. Research is aimed to understand how the compensatory response is positively associated with performance by demonstrating a positive association between the increased activations and successful performance on a task, rather than a negative association between non-selective over-recruitment and an inability to perform a particular task which might be associated with dedifferentiation.

Cabeza et al. (2002) reported that, in a source memory task, lower- functioning older adults were using the same network as younger adults (i.e., unilateral PFC activation) whereas high-functioning older adults showed a different pattern, recruiting left anterior PFC in addition to right anterior PFC. The results suggested that the "high" functioning older adults were capable of engaging a compensatory response through a reduction in hemispheric asymmetry during the source memory task (the most demanding task) whereas the "low" functioning older adults used the same network as younger adults, but ineffectively (Cabeza et al., 2002).

Rosen et al.'s (2002) fMRI study compared deep (semantic judgment: natural/man-made) and shallow (baseline judgment: uppercase/lowercase) encoding tasks across a group of younger adults and two groups of older adults, divided into "high" or "low" functioning groups based on performance on memory tests. Memory performance was better for young adults compared to both groups ("high" and "low") of older adults. The imaging results showed that "high" functioning older adults engaged left lateral and medial PFC activations similarly to young adults during semantic encoding and had greater activation compared to young adults in the right PFC during encoding. Older adults with "low" memory function scores had lower activations than those with "high"

functioning scores in all regions-of-interest (ROI), while the "high" older adults showed

increases in both left and right PFC activation compared to young adults, indicating

compensatory response in neural activity that is accompanied by equal or enhanced

performance on cognitive tasks.

Several theories have been posited regarding the etiology of the compensatory

response observed in older adults compared to young adults, including: (1) activations in

similar areas as those engaged by young adults but with a greater magnitude of

activation; (2) a more symmetric pattern of brain activity with additional activation in

homologous areas of the opposite hemisphere in the older adults; or (3) additional

activation of completely different areas. First, Cabeza (2002) conceptualized the bilateral

increases in activation as the Hemispheric Asymmetry Reduction in OLDer Adults

(HAROLD) model of cognitive aging, with evidence supporting the model coming from

multiple cognitive domains (for a review see Dennis & Cabeza, 2008).

According to Cabeza (2002), the bilateral frontal lobe activations in older adults

suggest that the brains of older adults work harder in order to counteract age-related

changes in brain structure and function. Therefore, older adults engage the brain in a

more distributed way relative to younger adults as a compensatory response, such that

there is an enhancement of cognitive performance (Cabeza, 2002). The compensatory

response as described by Cabeza in the HAROLD model should not be observed in

younger adults.

Moreover, age-related increases in frontal activity have also been accompanied by

decreases in posterior regions. Davis, Dennis, Daselaar, Fleck and Cabeza (2008) showed

that PFC activations that were positively correlated with cognitive performance in a

perception and a memory task were also negatively correlated with occipital activations. This result led to the proposal of a second compensatory pattern by Cabeza and colleagues termed the posterior-anterior shift in aging (PASA; Davis et al., 2008). For example, Gutchess et al. (2005) showed greater parahippocampal activation in younger compared to older adults when they were encoding pictures that were later correctly remembered, whereas older adults showed additional frontal activation for the items that were correctly remembered later on that was not present in younger adults. The PASA pattern suggests that older adults engage PFC to compensate for declines in posterior regions that mediate sensory processing. Similar patterns have been observed in studies investigating perception (Grady et al., 1994) and memory (Anderson et al., 2000; Dennis et al., 2007) among several cognitive domains (for a review see Cabeza & Dennis, 2013). Eyler, Sherzai, Kaup, & Jeste, (2011) showed that 66% of reviewed articles yielded positive correlations between brain function and cognitive performance supporting HAROLD or PASA.

Building on these ideas, Park and Reuter-Lorenz (2009) proposed an expanded conceptual theory of cognitive aging suggesting healthy cognitive aging involves reductions in brain volume and function paired with a functional reorganization, or "neural scaffolding." The Scaffolding Theory of Aging and Cognition (STAC) and their revised theory (STAC-r; Park & Reuter-Lorenz, 2014) posit that the aging brain engages in a compensatory response to the challenges posed by declining neural structure and function, similar to the HAROLD model. Additionally, STAC also posits that increases in bilateral activations can be seen when a task becomes more difficult as an adaptive brain response to any type of challenge. By this view, increases in fMRI activation

should be expected in all individuals, regardless of age, when they encounter a challenging task (Park & Reuter-Lorenz, 2009). For example, Leshikar et al.'s (2010) study of increased relational encoding demands in younger and older adults showed increases in left inferior frontal and left hippocampal activation in both groups. In their study, older and younger adults performed a task in which they encoded and retrieved semantically related and unrelated objects. Furthermore, Leshikar et al (2010) showed that the patterns of activations, i.e., networks used by older and younger adults, were largely the same as cognitive demands increased (Leshikar et al., 2010). Thus, consistent with STAC, the compensatory response has been observed in few studies in younger adults (See also Prakash et al., 2009).

The concept of task difficulty as a challenge that may elicit the compensatory response has been investigated by varying the load or number of items to be maintained while doing a working memory task. For example, using a verbal n-back task, Mattay et al (2006) showed that behaviorally, older adults performed as well as younger adults at a 1-back, but they showed decreases in performance at 2-back and 3-back. FMRI results showed older adults engaged bilateral PFC when performing the (1-back) working memory load, whereas under-activation was present as the task difficulty increased and when older adults performed more poorly (Mattay et al., 2006; see also Schneider-Garces et al., 2010; Cappell, Gmeindl & Reuter-Lorenz, 2010).

To accommodate the previous working memory findings', Reuter-Lorenz and Cappell (2008) proposed the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) which posits that older adults' processing inefficiencies cause the brain to engage more neural resources at lower levels of task demands. As demand

increases, however, older adults have limited resources available to process higher levels of the task and thus begin to show age-related decrements (Reuter-Lorenz & Lusting, 2005; Reuter-Lorenz & Cappell, 2008). There are relatively few studies consistent with the age-related CRUNCH's assumptions in other domains (see Morcom el al, 2007; Schneider-Garces et al.., 2009; Berlingeri et al., 2010; Berlingeri, Danelli, Bottini, Sberna & Paulesu, 2013; Toepper et al., 2014; Pagano, Fait, Brignani & Mazza, 2016).

Importantly, the inverted U shaped function predicted by CRUNCH has been observed in younger adults who have been categorized as low- and high-performing based on task performance. Nyberg et al. (2009) reported that high-performing younger adults compared to low-performing younger adults and older adults showed increases in activation in the thalamus and in the lateral prefrontal and parietal regions as the task became more difficult (3-back > 2-back > 1-back). In addition, low-performing younger adults showed increased activations in the thalamus and lateral prefrontal and parietal regions when difficulty increased (1-back < 2-back) which leveled off at 3-back. Older adults, however, showed increased activations in lateral prefrontal and parietal regions compared to young adults in the easiest condition (1-back) which leveled off at the two harder conditions (2-back and 3-back). These results suggest that some individuals can respond adaptively as cognitive demands increase and that some forms of adaptation may be utilized by both younger and older adults.

One problem in addressing this issue is that manipulating cognitive demands is not always easy or even possible in all cognitive domains. Research until now has relied on stimuli and tasks that make it difficult to separate the effects of task demands from performance. Task demands are generally manipulated by varying the number of items in

a working memory task (Schneider-Garces et al., 2009; Cappell et al., 2010), the number of items to be scanned in a visual search task (Ansado et al., 2013; Wiegand et al., 2014), the number of the previous presentations of materials needed to be studied, maintained and recalled (Morcom et al., 2007; Leshikar et al., 2010; Spaniol & Grady, 2012; Angel et al., 2016), value of the words to remember (Cohen et al., 2016), as well as manipulating response deadlines (Stern et al., 2012), memory load (Rypma & D'Esposito, 1999; Cairo et al, 2004; Zarahn et al., 2007; Park et al., 2009), or utilizing tasks with higher executive demands such as divided attention, inhibition, and switching (Prakash et al., 2009; Vallesi et al., 2010; Haung et al., 2012). Furthermore, most of these tasks are also inherently more demanding for older adults, including working memory (Mattay et al., 2006; Schneider-Garces et al., 2009; Cappell et al., 2010), working and prospective memory (Peira, Ziaei, & Persson. 2016), source memory (Cabeza et al, 2002; Morcom et al., 2007; Spaniol & Grady, 2012), episodic memory (Leshikar et al., 2010; Berlingeri et al., 2010; Berlingeri, et al., 2013) or attentional load (Ansado et al 2013; Wiegand et al, 2014). This makes it difficult to assess the degree to which the compensatory response is caused by age-related declines in brain structure and function, or if compensation is a more general age-invariant response to increases in task demands.

To adequately address this issue, it is critical to investigate the *compensatory response* using a task in which older adults do not show age-related declines such as general knowledge, vocabulary and lexical-semantic memory tasks (Verhaeghen, 2003; Wingfield & Grossman, 2006; Wierenga et al., 2008; Berlingeri et al., 2010). These tasks are particularly interesting because they may actually be more difficult for the younger adults who are being compared to older adults (Park et al., 2002; Hedden & Gabrieli,

2004). In fact, older adults sometimes outperform younger adults (Park et al., 2002) in lexical-semantic tasks (Rönnlund & Nillson, 2009; Kavé &Yafé, 2014; for a review see Harada, Natelson Love & Triebel, 2015).

The present fMRI study compares patterns of activations in young and older adults as task demand increased in two different tasks - an episodic retrieval memory task that is expected to be more difficult for older compared to young adults, and a lexical-semantic memory task that is expected to be more difficult for younger compared to older adults. Importantly, the two tasks were identical in every respect except for the type of memory judgment made by the participants. Difficulty was varied in both tasks by manipulating word-frequency. In the lexical-semantic task, in which participants decided whether two words were antonyms or synonyms, low frequency words are less familiar, making the task more difficult compared to high frequency words which are in common usage. We compared the lexical-semantic task to an episodic retrieval memory task, in which participants decided whether a pair of words had been recently encountered. Episodic tasks are often associated with decreases in performance in older adults (Park et al., 2002; Hedden & Gabrieli, 2004; Berlingeri et al. 2010, for a see review Craik & Rose, 2012). Difficulty in this task can also be manipulated by word frequency, since low frequency or uncommon words are more easily recognized compared to common, high frequency words (Schulman 1967; Shepard 1967).

Based on pilot work, the two tasks used in the present study were designed to be equivalent in overall level of difficulty. Task demands were manipulated using an objective, *a priori*, method of varying difficulty, rather than comparing two tasks that differ in complexity or using subsequent performance in the task itself to compare high

and low functioning groups of participants. Pilot testing ensured that the two levels of word frequency included in the study resulted in significant differences in difficulty in each task.

To our knowledge, the present study will be the first to examine the effect of the compensatory response using two tasks that share materials and general task requirements, where difficulty increases differentially for young and older adults. It's goal was to directly compare age-related differences in patterns of fMRI activation as cognitive demands increased for both lexical-semantic and episodic retrieval memory judgments in a within-subjects design.

Hypotheses in the present study were based on existing literature. First, regarding behavioral performance, we expected to confirm that older adults would outperform younger adults in the lexical-semantic task and that younger adults would have better episodic retrieval than older adults as difficulty increases. We also expected that high and low word frequency would differentially affect accuracy and reaction times in the two tasks – low frequency words will be more difficult in the lexical decision task, while low frequency words will be easier in the episodic retrieval task.

Regarding fMRI activation, if task difficulty determines the compensatory response as a general response that is age-invariant, we expect that older adults will show increases in fMRI activation during the episodic retrieval task, particularly when difficulty increases, while younger adults should show increases in fMRI activation during the lexical-semantic task as difficulty increases. If, however, the compensatory response is related to increasing age rather than task difficulty alone, we expect increases in activations in older adults compared to young adults in both tasks regardless of

difficulty. These age-related increases may be particularly evident in PFC, whereas fMRI

activations in young adults will be limited to regions known to be engaged for each task

(i.e., task-related), regardless of difficulty.

CHAPTER 2

2. Methods.

2.1. Participants.

A total of 24 young adults (17 females and 7 males) and 24 older adults (18 females and 6 males), recruited from the University of Arizona and local Tucson community, participated in the study. Students were recruited from upper-division classes or from an online experiment website for freshman as part of their requirements for their introduction to psychology class. Freshman participants were given course credit for volunteering, while the other participants received monetary compensation for their participation. The mean age was 72.13 years (5.37 SD; range 62-83) for the older group and 20.17 years (1.85 SD; range 18-24) for the young group. The older adults had significantly more years of education than the young participants (16.71 years, SD 2.34 versus 13.63 years, SD 1.74, respectively, $t(47)=3.36$, $p<.0001$), reflecting the fact that more than half of the older participants had completed a college degree. The study was limited to right-handed and native English speakers with normal or corrected-to-normal vision. Exclusion criteria included a prior history of neurological disorder, serious medical illness that could result in cognitive impairments, head trauma with sequelae, history of psychiatric disorder, current depression, and dementia or Mild Cognitive Impairment (MCI) diagnosis. Participants were also excluded if they were currently taking prescription medications with known cognitive effects (e.g., antipsychotics, Ritalin, Valium), if they had a history of drug or alcohol abuse, or if they had contraindications to MRI. All experimental procedures were approved by the University of Arizona Institutional Review Board.

Prior to the fMRI session, the older adults underwent a neuropsychological assessment to exclude cognitive deficits, which took place at the University of Arizona. Three areas of cognitive function were assessed, including memory, executive functions, and processing speed. Composite measures of memory and executive functioning were computed for each participant based on factor analysis methods described by Glisky and colleagues (Glisky and Kong, 2008; Glisky et al., 2001). The four tests contributing to the memory factor score were as follows: (1) Long- Delay Cued Recall from the California Verbal Learning task (CVLT), (2) Logical Memory I subtest, (3) Verbal Paired Associates I subtest, and (4) Face Recognition I subtest, all from the Wechsler Memory Scale-III (WMS-III). The five tests contributing to the executive function factor score were as follows: (1) correct number of categories achieved on the Wisconsin Card Sorting Test (WCST), (2) total number of words generated in a one-minute period for each letter of the FAS verbal fluency test, (3) the Mental Arithmetic subtest from the Wechsler Adult Intelligence Scale-R (WAIS-R), (4) the Mental Control subtest, and (5) the Backward Digit Span subtest from the Wechsler Memory Scale-III (WMS-III). In order to reduce the effects of cognitive interference, visual tasks were administered during the delays between verbal tasks. For each participant, test scores were transformed into z scores based on Glisky and Kong's (2008) normative sample of 227 older adults and were averaged to create two composite z scores for memory and executive functions. Neuropsychological testing lasted approximately three hours and was scheduled on a separate day from the fMRI session to avoid fatigue.

During the fMRI session, held at the University Medical Center, both older and younger adults underwent additional neuropsychological assessment including the Mini

Mental State Exam (MMSE; Folstein et al., 1975), the Geriatric Depression Scale (GDS; older adult group only) or the Beck Depression inventory (BDI-II; Beck et al., 1996; young adult group only), the vocabulary subtest from the Wechsler Abbreviated Scale of Intelligence (WASI), and the North American Adult Reading Test (NAART; Blair & Spreen 1989). Participants showed no symptoms of premorbid dementia or depression (all scores on MMSE greater than 26; all GDS or BDI-II scores less than 9). As *Table 2.1* indicates, the groups differed on both measures of vocabulary (WASI and NAART), with older adults performing significantly better than the younger adults.

Table 2.1. Comparison of younger and older adults on participant characteristics (means and standard deviations –SD).

	Young Adults	Older Adults	*p*-value
Age (years)	20.17 (1.85)	72.13 (5.77)	**< 0.0001**
Gender (F/M)	17/7	18/6	------
Education	13.63 (1.74)	16.71 (2.34)	**< 0.0001**
MMSE	29.63 (0.49)	29.13 (1.29)	*n.s.*
NAART	45.08 (8.17)	51.83 (4.57)	**0.001**
Vocabulary Subtest (WASI)	58.71 (10.14)	69.79 (6.28)	**< 0.0001**
BDI-II/MAS	2.38 (2.68)	2.67 (2.79)	*n.s.*

M, male; F, female, MMSE, Mini-Mental State Examination; NAART, North American Adult Reading Test; WASI, Wechsler Abbreviated Scale of Intelligence; BDI-II, Beck Depression inventory.

2.2. Materials and Tasks.

Stimuli used in both tasks were lists of word pairs, either synonyms or antonyms. The word pairs were categorized into one of two levels of difficulty based on word frequency using the Francis and Kučera (1982) norms. The high frequency word pairs contained commonly used words (e.g., damp-moist; curiosity-indifference), with a frequency range of 9 to 81 occurrences per million. The low frequency word pairs

included words with a frequency range of 0 to 7. The low frequency pairs contained words that are included in the preparatory manuals for the Graduate Record Examination (GRE; e.g., gorge-imbibe; garrulous-taciturn). During the pilot testing phase of the study, an independent group of 50 freshmen were tested to measure the difficulty of the word pairs. Participants were presented with a word pair on the computer screen and were asked to judge whether the words were "different" or "similar" in meaning. The pairs chosen following pilot testing were those that were correctly answered from the high frequency list with a mean of 90.89 (SD=5.91) and the low frequency list with a mean of 63.64 (SD=11.28). The final 152 word-pairs were randomly organized into two lists of pairs for each frequency level, each including 76 word-pairs (38 synonyms and 38 antonyms). It is important to note that words were never repeated and word pairs were matched for word length across word frequency. The average mean from the Francis and Kučera (1982) norms frequency analysis for the final high frequency list was 18.91 (SD= 8.4), and 1.19 (SD=1.42) for the low frequency list. The average word-length for the high frequency list was 7.4 (SD= 1.19) and 8.13 (SD=2.09) for the low frequency list.

The word lists were then used as stimuli for the two critical tasks presented in the MRI scanner, a lexical-semantic task and an episodic retrieval task, as well as a third vocabulary-knowledge task that was used to better assess participants' knowledge of the words after completing the fMRI scanning session. For the lexical-semantic task, participants were presented with a word pair on the computer screen and were asked to judge whether the words in the pair were synonyms- or antonyms; specifically, they were asked if the words in each pair had similar or opposite meanings. After the lexical-semantic task, participants completed an unexpected memory test. In the episodic

retrieval task, participants were presented with the previously-viewed word pairs from the lexical-semantic task interspersed with additional never-studied word pairs. Participants were asked to make a Yes-No forced-choice memory judgment for each of the word pairs, specifically, whether they saw the word pair during the previous different-similar judgment task. The lexical-semantic task always preceded the episodic retrieval task as the lexical-semantic task judgments served as the encoding phase for the episodic retrieval judgments. *Difficulty Load* in both tasks was manipulated based on word frequency. In the episodic memory task this is referred to as the word-frequency effect (WFE; also known as word frequency mirror pattern) where low frequency words are more likely to be recognized in episodic memory tasks, yielding higher hit rates and fewer false alarms than high frequency words (see Schulman, 1967; Shepard, 1967; Glanzer & Adams, 1985; Connine et al., 1990; Reder et al., 2000; Coane et al, 2011). In the lexical-semantic task, the easy level included the high frequency word pairs while the difficult level included low frequency word pairs in the episodic retrieval task.

In addition, as a control trial for both tasks that were presented in the scanner, participants were shown either "LEFT XXXXX" or "XXXXX RIGHT" on the screen, one at a time, and participants were required to press the left or right mouse button depending on the word presented. These trials provided a control for visual stimuli, motor preparation, and button press responses that were held constant in the two critical tasks.

In total, during the lexical-semantic task, participants were presented with 96 word pairs, of which 48 word pairs were randomly interspersed from each frequency level, along with an additional 40 control trials. Participants were not informed that they

would be tested for their memory for the word pairs later on as part of the episodic

retrieval task that followed immediately after the lexical-semantic task. While still in the

scanner, unexpected to participants, the episodic retrieval task followed immediately after

the lexical-semantic task. For the episodic retrieval task, participants were presented with

the 96 previously-viewed word pairs from the semantic judgment task interspersed with

an additional 48 lure or never-studied word pairs that included 24 word pairs randomly

interspersed from each frequency level divided into 12 synonyms and 12 antonyms. Lure

pairs were matched to the studied pairs on both frequency and word length.

2.3. Procedures.

After completing informed consent and metal screening and prior to entering the MRI

scanner, participants performed a practice session for the lexical-semantic task outside

the scanner to get them comfortable with the task. In the practice session, participants had

four trials (8 trials total) of each difficulty level (Difficulty Load: Easy and Difficult) and

four control trials in random order, each presented for 4 sec. with an inter-trial interval of

1 sec. Accuracy feedback was given to participants after each response. Participants

repeated the same practice session until they correctly answered all twelve items without

error, and the experimenter clarified instructions as needed to ensure they understood the

task.

Upon completion of the practice session, participants were placed supine in the

magnet wearing ear plugs and headphones to reduce noise with foam cushions around the

neck and head to minimize movement, a right-handed 3-button response mouse, and a

headset to communicate with the MRI technician. fMRI visual stimuli were projected

from a PC through VisuaStim digital high-resolution goggles (MR vision 2000 manufactured by Resonance Technologies, Inc., California). Behavioral responses and reaction times were collected using an MRI compatible mouse. Stimulus presentation was controlled by software (DMDX; version 2.4.06; Forster & Forster, 2003) that provides msec presentation accuracy and controls the onset of the scanner in order to temporally align image acquisitions, stimulus presentation, and response time data.

During the functional MRI procedures, participants were given two tasks. For both tasks, word pairs were presented in the scanner through viewing goggles (Resonance Technology, Inc.) placed over participants' eyes. Participants were asked to respond by pressing the assigned buttons from a 3 button MR-compatible mouse. In the lexical-semantic task, participants pressed one of 3 buttons on an MR-compatible mouse: the right button indicated that the words had similar meanings, the middle button indicated that the words had opposite meanings, and the left-most button was pressed if they did not know the meaning of the words. To decrease guessing, participants were instructed not to guess if they were unsure of the meanings of the words, but rather to press the left-most button indicating that they did not know the meaning.

Instructions for the episodic retrieval task were given verbally inside the scanner and upon completion of the lexical-semantic task. In the episodic retrieval task participants pressed the right button to indicate Yes (i.e., they had seen the word pair the previous task) and the middle button to indicate No (i.e., they had not seen the word pair in the previous task). Participants were instructed not to press the left-most button during this task.

For the control trials included in both tasks, participants were instructed to press left-most button when 'XXXX left' was presented on the screen (50% of the cases) and the right-most when 'right XXXX' was presented on the screen.

In both tasks, all word pairs and control trials were presented for 4 sec. with an intertrial interval of 0.5 sec, 1 sec or 1.5 sec, so that the duration of the experimental stimuli was held constant across participants while the onset of experimental trials was jittered to facilitate deconvolution of the hemodynamic response.

Functional and structural imaging lasted approximately 50 minutes (including breaks); participants completed five functional scans in sequence: two scans for the lexical-semantic task, each with a duration of 5 min, 40 sec. followed by three scans of the episodic retrieval task, duration of 5 min, 32 sec. each. Before the start of each scan, participants were reminded verbally of the instructions for the task they would be performing.

Participants were removed from the scanner and completed the vocabulary-knowledge task in order to assess their knowledge of the specific materials presented in the two previous experimental tasks. In the vocabulary-knowledge task, all word pairs, regardless of whether they were previously tested as synonyms or antonyms, were presented in a multiple choice, self-paced test where the participants were asked to indicate the correct meaning of the word pair from 3 alternatives. For example, for the word pair "cheap-costly," participants could choose the definition (for example, "how much something is worth?") from three choices that included two incorrect answers ("an attitude towards interacting with others" or "how natural something is?"). Alternatively, they could respond, "Don't know," or they could choose the "Other" option where the

participant could write their own definition. Participants were debriefed, thanked for their

participation, and given research credits or monetary compensation for their time.

2.4. fMRI Methods.

2.4.1. Data Acquisition.

Images were collected in a one-hour session on a GE 3.0T Signa Excite system

with an 8-channel phased array coil. A 3-plane localizer was collected for image

alignment, followed by a whole brain 3D spoiled echo gradient-echo MRI (3DSPGR)

series (1.5-mm sections covering the whole brain, TR= 5.1ms, TE= 2ms, TI= 500ms, flip

angle= 15º, matrix= 256 X 256, FOV= 26cm). Functional MRI scans were acquired using

a single-shot spiral pulse sequence to obtain inward and outward spiral data sets (Glover

and Law, 2001) that were combined during post-processing using a weighted average.

Sections were aligned axially along the AC-PC plane, covering the whole brain,

TR=2,040 ms, TE=30msecs, flip angle=90, matrix 64x64, 3.8mm sections, no skip.

2.4.2. Data Processing.

Functional images were analyzed using Statistical Parametric Mapping (SPM8)

software (Wellcome Department of Cognitive Neurology, London, UK;

http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Images for each participant were

corrected for asynchronous slice acquisition (slice timing: reference slice = 16, TA =

2.03) and then realigned to the third volume of each scan for motion correction. Spatial

normalization parameters were estimated by warping each participant's mean functional

image to the SPM8 MNI (Montreal Neurological Institute) EPI template (Ashburner &

Friston, 1999). The normalized images were resliced to 3-mm cubic voxels and smoothed with an isotropic 7 mm full-width-at-half-maximum (FWHM) Gaussian kernel. A high-pass filter was applied to the data to exclude low-frequency components of the fMRI signal from analysis. Resulting images were visually inspected for artifacts and adequacy of realignment.

2.4.3. fMRI Data Analyses.

Statistical analyses were performed at the single-subject level using a general linear modeling approach (GLM). The hemodynamic response (HDR) for each trial was modeled using a canonical hemodynamic response function. Estimation of the HDR was modeled using the onset time of trials with durations equal to zero. Only correct trials for each condition were included in the analyses. Incorrect trials and trials for which the participant did not respond within the time limit were modeled separately as conditions of no interest. Statistical parametric maps were calculated to create contrast images comparing HDR estimates for the experimental conditions of both tasks. Parameter estimates for each trial type were calculated at each voxel to create a single contrast image for each participant and each condition. Random effects analyses were conducted to create two unique models for each of the tasks separately. The first model generated individual contrast images for each individual condition. The second model calculated linear increases as a function of difficulty load by including a first order polynomial expansion in the analysis model. The correct trials for both levels of the tasks were modeled using parameter 1 to signify Easy trials and parameter 2 to signify the Difficult trials. The resulting first level contrasts for both models were entered into the second-

level analysis to investigate group level effects aimed to identify: *task-related* activity, *task-general* activity, *task-specific* activity and activity associated with linear increases as a function of difficulty.

Following the first-level model specification, planned group level analyses were conducted in a series of steps: 1) One-sample T-Tests in each group separately aimed to examine patterns of activation associated with *task-related* accuracy in both tasks (i.e., correct lexical-semantic judgments > controls or hits in the episodic retrieval task > controls) regardless of difficulty. 2) To compare the two experimental tasks, we conducted a conjunction analyses to identify regions of significant overlap or *task-general* activity between correct lexical-semantic judgments and hits in the episodic retrieval task (One-Way ANOVA) in each group separately. Note that the maps resulting from these conjunction analyses were used as inclusive masks in the next analyses (each contrast image was thersholded to $p < 0.05$, FDR corrected, k=50, resulting in a joint probability of $p < 0.0025$, FDR corrected); 3) To investigate *task-specific* activity *across* both tasks we conducted one-sample T-Tests (i.e., correct lexical-semantic judgments > hits in the episodic retrieval task or hits in the episodic retrieval task > correct lexical-semantic judgments) for each group separately. The maps resulting from these analyses were thersholded in a more lenient threshold p <0.01, uncorrected, k > 10. After the masked procedure, the resulting probabilities are not independent, therefore the joint probability reported was greater for each significant peak-level yielding at least a p<0.01, uncorrected $Z \geq 2.41$; Nichols, Brett, Andersson, Wager, & Poline, 2005); 5) Finally, the analysis aimed to identify the linear increases as a function of difficulty were conducted on the maps resulted from the first order polynomial expansion in the analysis model

separately for the younger and older adults in both tasks masked inclusively. Note that the maps resulting from the conjunction analyses (previously described in step #2) were used as inclusive masks in the follow-up analyses using a more lenient threshold $p < 0.01$, uncorrected. Therefore, after the masked procedure, the resulting probabilities are not independent, therefore the joint probability reported was greater for each significant peak-level yielding at least a $p < 0.01$, $Z \geq 2.41$ and a corrected cluster significance threshold of $p < 0.01$; Nichols et al., 2005); 6) Lastly, we examined age-related differences in linear increases as a function of difficulty by conducting an independent samples t-tests to test for group differences in regions of activation. For all the linear increases due to difficulty analyses, Monte-Carlo simulations, with 10,000 replicates and alpha level of .01, were conducted on the group brain mask to obtain corrected, cluster level thresholds. Multiple-testing of spatially correlated data (Forman et al., 1995) with their significant thresholds for all the linear increases as a function of difficulty analyses described above results were thresholded at $P_{voxel} < 0.01$ based on Monte Carlo simulations (3dClustSim, AFNI, http://afni.nimh.nih.gov) and clusters were deemed significant in the lexical-semantic task with a minimum of 159 contiguous voxels and for the episodic retrieval task with a minimum of 163 contiguous voxels.

To further characterize the BOLD response, we conducted Region of interest (ROI) analyses using MarsBaR (release 0.44; http://marsbar.sourceforge.net/ ; Brett, Anton, Valabregue, & Poline, 2002). Follow-up ROI analyses were performed for significant clusters in the group contrast analyses, using a 5-mm sphere drawn around the peak voxel for each cluster. All voxels within the sphere were averaged and extracted to form a single measure of activation for each individual and each ROI. The mean

parameter estimate across all significant voxels was extracted for the two levels of difficulty of each task greater than controls contrasts, respectively. Parameter estimates were extracted and exported to SPSS (IBM® SPSS® Statistics 23.0) for additional analyses.

Finally, in order to investigate the relationship between behavioral performance and brain activation, we performed correlation analyses (Pearson's correlation coefficient) on the BOLD signal estimates extracted from selected ROIs and accuracy and RT measures and neuropsychological measures for younger adults and older adults. Stereotactic coordinates were generated in the standard Montreal Neurological Institute (MNI) brain by SPM, and are reported here in MNI space. Figures were created using MRIcron (version 7; http://www.cabiatl.com/mricro/mricron/index.html).

3. Results.

3.1. Behavioral Performance.

The behavioral results are displayed in *Table 3.1*. For all behavioral tasks, 2X2 mixed

design ANOVAs were conducted comparing Age Group (Younger, Older) as the

between-subjects factor and Difficulty Load (Easy, Difficult) as the within-subjects

factor.

Table 3.1. Behavioral performance of each group -Means and Standard Deviations.

	Condition	Young Adults	Older Adults
Vocabulary-knowledge task			
Accuracy Ratio	Easy	1.04 (0.12)	1.04 (0.06)
(lexical-semantic /	Difficult	1.09 (0.12)	1.06 (0.8)
Vocabulary-knowledge)			
Lexical-semantic task			
Accuracy	Easy	0.94 (0.08)	0.91(0.08)
	Difficult	0.72 (0.16)	0.79 (0.11)
Reaction Times	Easy	1886.85 (302.27)	2106.48 (295.61)
(msec)	Hard	2347.79 (335.57)	2385.79 (320.70)
Do not know	Easy	0.003 (0.007)	0.008 (0.013)
	Difficult	0.125 (0.147)	0.053 (0.062)
Reaction Times	Easy	476.55 (1100.59)	1006.25 (1468.52)
(msec)	Difficult	2071.15 (1259.46)	1885.78 (1530.72)
Episodic retrieval task			
Accuracy	Easy	0.87 (0.12)	0.77(0.13)
	Difficult	0.89 (0.08)	0.72 (0.17)
Reaction Times	Easy	1540.32 (226.84)	1866.80 (333.73)
(msec)	Difficult	1466.81 (214.59)	1836.50 (296.20)
False Alarms	Easy	0.06 (0.08)	0.15 (0.13)
	Difficult	0.09 (0.11)	0.22 (0.17)
Reaction Times	Easy	1452.36 (1046.12)	1767.38 (1110.27)
(msec)	Difficult	1423.07 (914.78)	1757.54 (872.74)
Discrimination Index	Easy	2.77 (0.83)	2.01 (0.84)
(D Prime)	Difficult	2.68 (0.70)	1.55 (0.88)

Note: Standard Deviations in parenthesis.

3.1.1. Vocabulary-knowledge task.

Performance in the vocabulary-knowledge task was used to establish the success of the difficulty load manipulation in the lexical-semantic task. Knowledge of word pairs was measured by the final vocabulary-knowledge task that participants completed outside the scanner. Only items that were also given the correct true definition in the final vocabulary-knowledge task were included in the behavioral and the subsequent fMRI analyses for the lexical-semantic task. We calculated a ratio of each participant's number of correct responses in the vocabulary-knowledge test to each participant's number of correct responses in the lexical-semantic judgment task (see *Table 3.1*). A ratio of 1 indicates a perfect correspondence between correct lexical-semantic judgments and correct responses in the final vocabulary-knowledge task. A ratio above 1 would indicate that participants responded correctly to more items in the self-paced vocabulary-knowledge task than in the lexical-semantic task. Results suggested that both groups had excellent correspondence between accuracy scores with no differences across group or difficulty load (F's <1).

3.1.2. Lexical-semantic task.

Accuracy was defined as the proportion of correct judgments/total number of pairs presented in the lexical-semantic task. Both younger and older adults were more accurate at judging the Easy pairs than the pairs in the Difficult condition, indicated by a main effect of difficulty load [$F(1, 46) = 83.94$, $p < 0.0001$, $\eta_p^2 = 0.64$]). Both groups performed overall similarly (main effect of Group [$F(1, 46) = 0.59$, *n.s.*, $\eta_p^2 = 0.01$]) in

the task. However, a group by difficulty load interaction [F (1,46)= 8.39, p < 0.05, $\eta_p^2 =$ 0.15] confirmed our hypothesis that younger adults were disproportionately less accurate at identifying the correct lexical-semantic judgments in the Difficult condition than the Easy condition, compared to older adults[1]. Follow-up analysis showed a trend towards significance such that older adult's responses were more accurate than younger adults in the Difficult condition, [t(46)= -1.85, p=0.07], whereas in the Easy condition no difference between the groups was observed, [t46)= 1.30, $n.s.$].

As a way to ensure that participants were responding only to items they were sure of, we compared the proportion of "do not know" responses. Both groups responded with more "do not know" in the difficult condition than in the easy condition (main effect of difficulty load [F (1,46)= 28.84, $p < .0001$ $\eta_p^2 = 0.38$]). As with the correct judgments, both groups equally chose the "don't know" responses (main effect of group [F (1,46)= 3.63, $n.s.$, $\eta_p^2 =0.07$]). Once again, an interaction between difficulty load and group was observed [F (1, 46) = 6.06, p < 0.05, $\eta_p^2 = 0.11$][2]. Younger adults tended to used more "don't know" responses in the Difficult condition [t(31.12)= 2.17, p<0.05] than in the Easy condition [t(36.98)= -1.61, $n.s.$] compared to older adults.

3.1.3. Episodic retrieval task.

Accuracy judgments for the Easy and Difficult conditions (measured by

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[1] Note that a similar ANOVA carried out to the accurate lexical-semantic judgments Reaction Times (RT) provided an identical pattern of results.
[2] Again, the similar ANOVA carried out to the "do not know" RT provided an identical pattern of results.

proportion correct) did not differ (Difficulty load main effect [$F(1,46)= 1.07$, *n.s.*, $\eta_p^2 = 0.23$]). Older adults performed less accurately overall than younger adults in both conditions (main effect of group [$F(1,46)= 14.50$, $p < 0.0001$, $\eta_p^2 = 0.24$]) and as expected, the group by difficulty load interaction reached significance [$F(1,46)= 5.17$, $p < 0.05$, $\eta_p^2 = 0.10$][3]. The post-hoc exploration of the inteaction indicated that older adults were disproportionately less accurate at recognizing old pairs in the Difficult condition compared to those in the Easy condition [$t(23) = -2.89$, $p = 0.008$] than the younger adults [$t(23) = -0.75$, *n.s.*].

Older adults responded with more false alarms compared to younger adults [main effect of group; $F(1,46)= 9.39$, $p < 0.05$, $\eta_p^2 =0.17$], and both groups produced more false alarms in the Difficult condition than in the Easy condition [main effect of Difficulty load ; $F(1,46)= 12.90$, $p = 0.001$, $\eta_p^2 =0.21$], with no significant interaction [$F(1,46)= 2.20$, $p < $ *n.s.*, $\eta_p^2 =0.04$][4].

Because accuracy and false alarms yielded different patterns, D Prime scores were calculated for each participant. D Prime scores were calculated using Brophy's (1986) formula (https://memory.psych.mun.ca/models/dprime/index.shtml). Accuracy and false

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[3] The results of the ANOVA carried out for the accuracy RT responses were different than for the accuracy results. Participants responded faster in the Difficult condition than when responding in the easier Easy condition, yielding a significant main effect of difficulty load [$F(1,46)= 6.72$, $p =0.05$]. Also, older adults were disproportionaly slower in both conditions of the task than younger adults with a significant main effect of Group [$F(1,46)= 20.96$, $p < 0.0001$] but the interaction Group by Difficulty Load was not significant [$F(1,46)= 1.16$, $p < $ *n.s.*].
[4] A similar ANOVA carried out for the false alarms RT showed that neither the interaction of Group by Difficulty Load or the simple main effects were significant, *F*'s < 1, *n.s.*

alarms scores were first adjusted using the standard method described by Wixted and Lee

(n.d., Retrieved from http://www.kangleelab.com/signal%20detection%20theory.html)

for participants perfect performance (i.e., (0) false alarms or (100%) hits; see also Hautus,

1995). Accuracy (measured by the discrimination index) suggested lower D prime scores

in the Difficult condition than in the Easy condition (main effect of Difficulty load [F

$(1,46)= 9.28$, $p < 0.05$, $\eta_p^2 =0.17$]). Older adults had lower D Prime scores than younger

adults in both conditions (main effect of Group [F $(1,46)= 9.28$, $p < 0.0001$, $\eta_p^2 =0.28$]).

As depicted in the scatter plots for young and older adults in *Figure 3.1*, a Group by

Difficulty Load interaction [F $(1,46)= 4.44$ $p = 0.04$, $\eta_p^2 =0.08$] was observed, indicating

that older adults had a larger decrease in D prime in both conditions than younger adults.

Follow-up t-tests suggest the difference D prime scores between the Difficult and Easy

conditions was significant for the older adults [$t(23)= 4.18$, $p<0.0001$] but not for the

younger adults [$t(23)= 0.65$, *n.s.*].
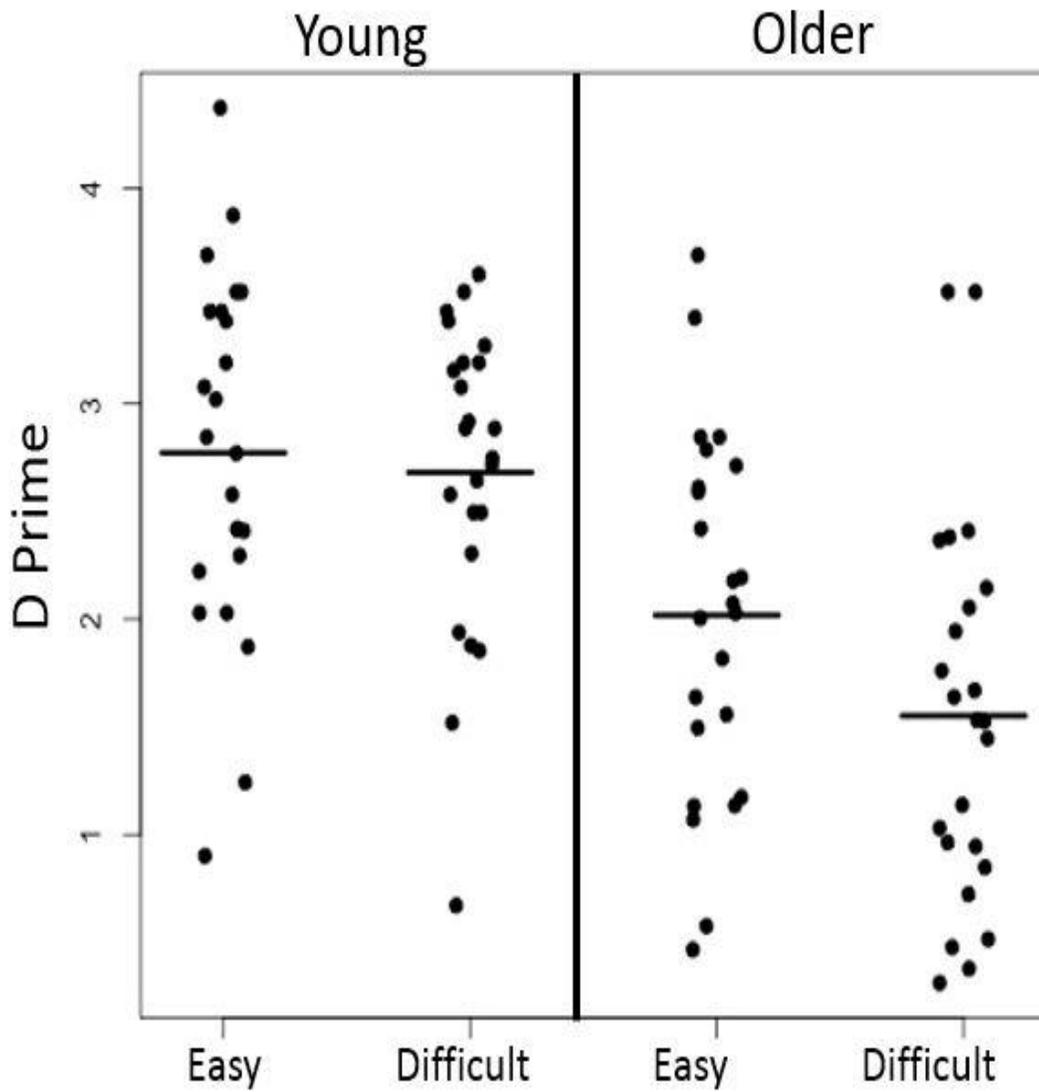
Figure 3.1. Scatter plots of *d* prime scores for the episodic retrieval task conditions. Older adults were significantly impaired relative to younger adults on both conditions of the task, but worse in the difficult version of the task.

3.2. fMRI Results.

3.2.1. Brain activity associated with successful task-related activity

(Experimental conditions versus controls).

To assess the brain regions that were uniquely engaged during successful retrieval compared to the control condition across difficulty load, in both tasks, we compared activations between correct lexical-semantic judgments > controls and hits in the episodic retrieval task > controls first using a within group random effects approach. Note that the controls used for each of the contrasts of interest were the controls specific to the task of comparison. For each age group, regions of significant successful task-related activation in each task relative to controls were identified using a threshold of $p < 0.0025$, FDR corrected, and a cluster extent of k = 10 voxels. *Figure 3.2* and *Figure 3.6* contains the within group random effects (successful task-related activity > controls) results for young and older adults, respectively, for the lexical-semantic task (see also *Table 3.2*) and the episodic retrieval task (see also *Table 3.3*).

Successful Lexical-semantic task-related activity.

For both groups, as expected, the lexical-semantic task activated regions that are typically associated with verbal semantic processing, including regions of left frontal cortex and temporal cortices typically involved in lexical processing, including the superior temporal gyrus, medial frontal gyrus, inferior frontal gyrus, fusiform gyrus and medial temporal regions (hippocampus and parahipocampal gyrus). Analyses in both groups also showed occipital and motor regions involved in viewing and responding to the stimuli, respectively, as well as robust activations in subcortical regions including the

thalamus, midbrain, caudate, putamen, and anterior cerebellum. The lexical-semantic task showed nearly identical patterns of whole-brain activation consistent with previous reviews of semantic processing regions described by Binder et al. (2009) including robust engagement of left ventromedial prefrontal cortex (VMPFC)/inferior frontal gyrus (IFG) orbital parts, IFG including operculum and triangular parts, lateral and ventral temporal regions, dorsomedial PFC (DMPFC) including the medial prefrontal cortex/supplementary motor area (SMA) and pre-SMA/superior frontal gyrus, and bilateral parietal regions and posterior cingulate (for review see Binder and Desai, 2010).

Successful Episodic retrieval task-related activity.

Both groups activated extensive regions consistent with previous fMRI episodic memory retrieval studies (Wiggs et al., 1998; Kensinger et al., 2003; Patterson, Nestor & Rogers, 2007; Burinova & Grady, 2007; Burianova, McIntosh & Grady, 2010; Hoscheidt et al., 2010) including the hippocampus, bilateral superior temporal gyrus; bilateral superior, medial, middle and inferior prefrontal cortex, and areas of the ventral visual stream including primary visual cortex, posterior temporal-occipital gyrus, and fusiform gyrus, as well as bilateral superior parietal lobule, precuneus and posterior cingulate.

Although less extensive, regions of activation engaged by younger adults mirrors the regions elicited in older adults, and this was evident for both experimental tasks. Interestingly, consistent with many fMRI studies of aging, older adults showed a greater extent of activations in task-related regions compared to younger adults (Grady et al., 1994; Cabeza et al., 2002; Park et al., 2010). Moreover, the greater extent of activations in older adults showed a tendency to predominantly engage bilateral brain regions.

A. Lexical-Semantic Task

Young

Older

Conjunction

Z= -16   -8   0   8   16   24   32   40   48   56   64

B. Episodic Retrieval Task

Young

Older

Conjunction

Z= -16   -8   0   8   16   24   32   40   48   56   64
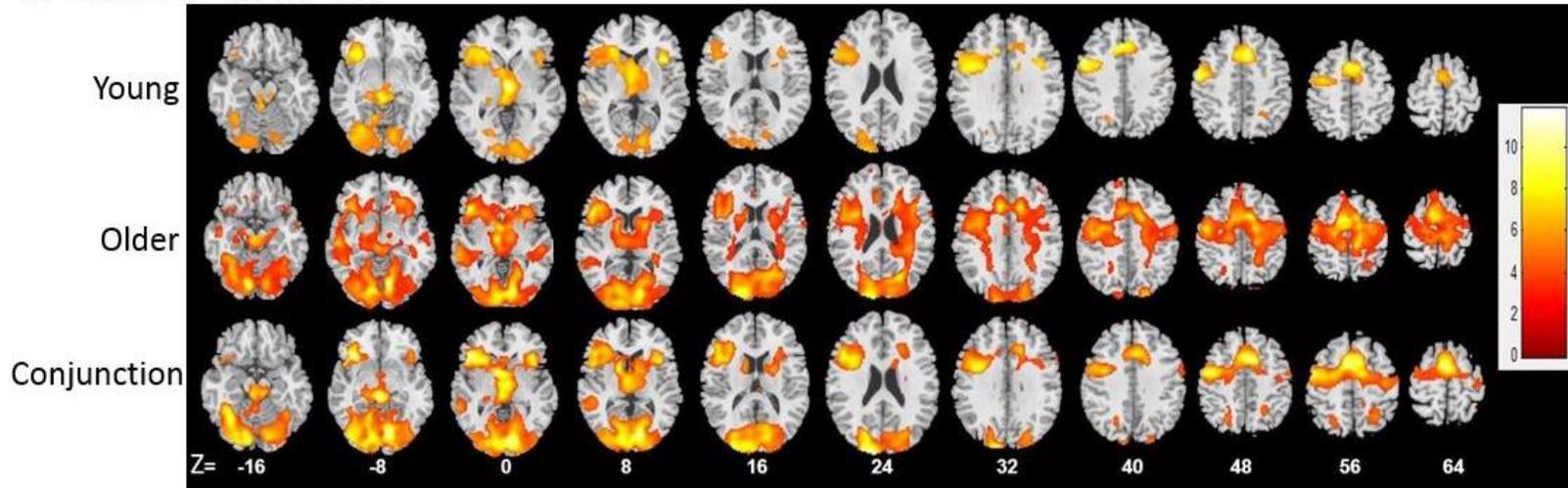
Figure 3.2. Patterns of brain activation during encoding A) lexical-semantic task B) episodic retrieval task for both Young, Older and the conjunction results across both age groups. All results are displayed on axial slices of a single brain spatially normalized to MNI space.

Table 3.2 Regions of whole brain activity in MNI coordinate space showing the patterns of activation in the **lexical-semantic task** (correct judgments > controls) for A) Younger Adults, B) Older Adults and C) across all participants (conjunction analysis).

Region	H	MNI Coordinate x	y	Z	Cluster Size (k)	*T*-value
A. Young Adults						
Subcortical						
Thalamus	R	2	-12	-2	13839△	10.27
Caudate	L	-2	2	6	△	7.26
	R	24	2	18	41	4.73
Frontal						
Suppl. Motor Area (SMA)	L	0	12	52	1654*	8.02
	R	10	-6	56	*	5.51
Inf. Frontal Gyrus (IFG)						
- Orbital	L	-34	28	-4	△	7.85
- Triangular	L	-44	30	2	△	6.55
- Operculum	L	-58	16	26	△	6.61
Insula	L	-28	28	6	△	7.40
	R	38	18	8	561	8.35
Middle Frontal Gyrus (BA 6)	L	-38	-6	52	△	6.56
Cingulate Cortex (BA 32)	R	12	24	34	*	4.84
Temporal						
Fusiform Gyrus	L	-30	-70	-6	△	6.78
Hippocampus	L	-20	-28	-8	△	5.65
Mid. Temporal Gyrus (MTG)	L	-60	-32	6	35	4.39
Occipital						
Occipital G.-Sup., Mid., Inf.	L	-19	-97	27	△	6.81
-Inf.	R	28	-84	-12	△	5.03
Lingual Gyrus (BA 18)	L	-30	-86	-14	△	5.47
	R	12	-76	-10	△	6.22

△ indicates continuous voxels from cluster size: 13839;
* indicates continuous voxels from cluster size: 1654

Region	H	MNI Coordinate x	y	z	Cluster Size (k)	*T*-value
B. Older Adults						
Subcortical						
Thalamus	L	-8	-10	-2	∞	9.65
Caudate	L	-4	2	0	∞	9.51
Putamen	R	26	24	-4	∞	9.42
Frontal						
Suppl. Motor Area (SMA)	L	-10	0	60	∞	11.73
	R	10	8	50	∞	11.75
Cingulate Cortex	L	-10	20	36	∞	10.46
Inf. Frontal G. (IFG)						
- Triangular	L	-46	28	0	∞	11.42
- Orbital	L	-36	26	-10	∞	9.57
	R	28	34	-8	∞	7.43
- Operculum	L	-34	4	26	∞	9.42
	R	38	12	26	∞	7.87
Sup. Frontal Gyrus (SFG)	L	-13	51	41	85	4.76
	L	-16	58	26	13	4.62
Insula	L	-24	10	-18	∞	3.88
	R	34	24	-4	∞	7.45
Middle Frontal Gyrus	R	36	40	30	30	4.21
Temporal						
Mid. Temporal Gyrus (MTG)	L	-60	-22	-4	∞	9.96
Fusiform Gyrus (BA 37)	L	-40	-44	-20	∞	9.79
Hippocampus	L	-22	-12	-12	∞	6.44
	R	18	-12	-16	∞	6.91
	R	38	-12	-26	42	4.64
Rolandic Operculum	R	64	-8	12	90	4.81
Sup. Temporal Gyrus (STG)	L	-40	-44	8	∞	4.06
	R	34	-38	10	∞	5.93

Table 3.2 Continued…

Region	H	MNI Coordinate			Cluster Size (k)	T-value
		x	y	z		
Parietal						
Precuneus	L	3	-75	19	∞	7.51
	R	22	-50	46	∞	6.58
Occipital						
Lingual Gyrus	R	10	-76	-10	61419∞	13.88
	L	-12	-80	-14	∞	13.08
Occipital G.-Sup., Mid., Inf.	L	-12	-98	14	∞	11.45
Cuneus	R	14	-92	20	∞	8.22

∞ indicates continuous voxels from cluster size: 61419.

C. Conjuction Analysis Across All Subjects						
Subcortical						
Thalamus	L	-4	-28	-6	39754†	7.82
	R	4	-12	-2	†	6.49
Caudate	L	-2	2	2	†	6.66
	R	6	4	2	†	5.71
Frontal						
Suppl. Motor Area (SMA)	R	8	10	50	†	7.46
Inferior Frontal Gyrus (IFG)	L	-52	16	-6	†	5.55
- (BA 9)	L	-36	4	30	†	6.23
- Triangular	L	-46	28	0	†	7.41
- Orbital	L	-36	24	-10	†	7.37
- Operculum (BA47)	L	-50	14	8	†	5.26
- Operculum	R	38	6	32	†	2.86
Insula	L	-26	22	0	†	5.92
	R	38	18	6	†	5.73
Sup. Frontal Gyrus (SFG)	L	-20	-8	54	†	5.00
	R	16	-8	76	#	2.54
Cingulate Cortex (BA 32)	R	8	24	36	†	4.90
Precentral Gyrus (pre-SMA)	R	24	-14	78	32#	2.61
Temporal						
Sup. Temporal Gyrus (STG)	L	-60	-40	4	604	4.94
Hippocampus	L	-18	-26	-8	†	3.92

Region	H	MNI Coordinate			Cluster Size (k)	T-value
		x	y	z		
Parietal						
Sup. Parietal Lobule (BA 7)	L	-23	-63	45	323	3.80
Inf. Parietal Lobule	R	26	-48	52	316	3.21
Precuneus	R	12	-42	56	21	2.77
Occipital						
Lingual Gyrus	L	-28	-90	-14	†	5.49
	R	10	-78	-10	†	7.69
Calcarine Sulcus	L	-10	-76	10	†	5.49
	R	10	-84	4	†	7.51

† indicates continuous voxels from cluster size: 39754;
# indicates continuous voxels from cluster size: 32

Region, anatomical region defined by MNI (Montreal Neurological Institute) coordinates in x, y, z, planes; H, hemisphere; L, left; R, right; Sup, superior; Mid, Middle; Inf, Inferior; SMA, Supplementary Motor Area; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus; BA, Brodmann Area; MTG, Middle. Temporal Gyrus; STG, Superior Temporal Gyrus. Results at a significance threshold of $p<0.05$ FDR corrected, with a 10-voxel cluster extent threshold.

Table 3.3. Regions of whole brain activity in MNI coordinate space showing the patterns of activation in the **episodic retrieval task** (hits > controls) for A) Younger Adults, B) Older Adults and C) across all participants (conjunction analysis).

A. Young Adults

Region	H	X	y	Z	Cluster Size (k)	T-value
Subcortical						
Thalamus	L	-10	-16	12	△	6.55
	R	14	-12	6	1970△	6.88
Caudate	R	20	0	18	△	5.91
Putamen	L	-22	16	-2	††	4.62
Frontal						
Medial Frontal Gyrus	L	-4	22	48	2025†	7.95
-includes SMA	R	6	24	46	†	7.42
Precentral Gyrus	L	-38	-8	54	580	6.01
Inf. Frontal Gyrus (IFG)						
- Operculum	L	-38	16	20	∞	5.91
- Operculum (BA 9)	R	56	20	36	212	7.09
- Triangular	L	-38	14	26	1021∞	6.05
- Orbital Part (BA 47)	L	-34	32	-6	576††	5.51
Insula (BA 13)	L	-34	20	6	††	5.13
	R	36	20	-6	167	5.71
Cingulate Cortex	L	-4	2	28	84	5.03
Temporal						
Hippocampus	L	-21	-31	-5	△	4.77
	R	22	-26	-6	△	5.23
Fusiform Gyrus	L	-44	-42	-22	*	5.20
Mid. Temporal Gyrus (MTG)	L	-52	-32	4	59	5.61
Parietal						
Sup. Parietal Lobule	L	-26	-66	48	294	5.72
-includes Angular Gyrus	R	30	-66	48	64	5.12
Paracentral Lobule (BA4)	R	8	-42	66	113	5.45
Precuneus	L	-8	-78	38	21	4.72
Posterior Cingulate Cortex	L	-8	-32	24	45	4.73
- includes retrosplenial	R	12	-38	28	10	4.61
Occipital						
Lingual Gyrus	L	-8	-78	4	6907*	6.96
Occipital G.-Sup.,Mid.,Inf.	L	-32	-80	-8	*	5.81

△ indicates continuous voxels from cluster size: 1970;
† indicates continuous voxels from cluster size: 2025;
∞ indicates continuous voxels from cluster size: 1021;
†† indicates continuous voxels from cluster size: 576;
* indicates continuous voxels from cluster size: 6907.

B. Older Adults

Region	H	x	y	Z	Cluster Size (k)	T-value
Subcortical						
Caudate	L	-18	26	4	‡	7.69
	R	14	14	2	‡	7.85
Putamen	L	-20	-2	12	‡	4.57
	R	24	10	6	‡	6.81
Thalamus	L	-4	-8	-2	‡	6.28
	R	6	-8	0	‡	6.70
Cerebellum Ant. Lobe	R	22	-48	-38	11	5.48
Frontal						
Sup. Medial Frontal Gyrus	L	-7	53	29	113	5.24
Inf. Frontal G. (IFG)						
- Triangular	R	32	30	2	‡	10.10
- Orbital Part	R	38	20	-14	‡	5.50
Insula	L	-32	22	0	‡	9.36
	R	34	22	2	‡	8.87
Cingulate Cortex	L	-16	22	30	‡	9.28
Medial Frontal Gyrus	L	-4	12	50	‡	7.87
-includes SMA						
Middle Frontal Gyrus (BA 9)	R	46	20	30	‡	7.31
Temporal						
Mid. Temporal Gyrus (MTG)	L	-60	-38	-4	‡	6.53
Inf. Temporal Gyrus (IFG)	L	-48	-38	-18	‡	6.17
	R	46	-70	-12	‡	4.78
Hippocampus	R	16	-12	-10	‡	5.46
Sup. Temporal Gyrus (STG)	R	54	-22	-2	178	5.07
Parietal						
Inf. Parietal Lobule	L	-26	-66	44	‡	4.41
Posterior Cingulate Cortex	L	-4	-34	32	98	4.71
Precuneus	L	-8	-36	56	‡	4.53
	R	20	-50	46	‡	4.52
Occipital						
Calcarine Sulcus	L	-10	-84	10	‡	8.77
	R	16	-86	0	48938‡	12.46
Occipital G.-Sup.,Mid.,Inf.	L	-14	-92	18	‡	11.51

‡ indicates continuous voxels from cluster size: 48938

C. Conjuction Analysis. All Subjects

Region	H	x	y	Z	Cluster Size (k)	T-value
Subcortical						
Thalamus	R	14	-12	8	□	5.48

Table 3.3 Continued…

Region	H	MNI Coordinate			Cluster Size (k)	T-value
		x	y	Z		
Frontal						
Sup. Frontal Gyrus (SFG)	R	22	56	0	14	2.72
Sup. Medial Frontal Gyrus	R	8	22	44	□	6.91
Middle Frontal Gyrus	L	-33	27	21	□	5.22
	R	32	28	24	□	3.34
Insula	L	-30	-24	18	13	2.44
Inferior Frontal Gyrus	L	-36	20	-2	□	5.85
	R	36	20	-6	□	5.49
- Triangular	L	-42	14	28	□	5.85
	R	42	20	28	□	3.95
-Operculum (BA 44)	L	-52	16	14	□	4.01
- Operculum	R	54	14	36	□	4.90
Cingulate Cortex (BA 32)	L	-2	26	36	□	5.27
Precentral Gyrus	R	44	-26	68	11	2.56
Temporal						
Hippocampus	R	24	-26	-6	□	3.25
Sup. Temporal Gyrus (STG)	R	40	-28	12	82	3.26
Parietal						
Sup. Parietal Lobule	L	-26	-66	44	□	4.70
Precuneus	L	-10	-40	62	□	3.49
	R	20	-46	50	□	4.11
Occipital						
Occipital –Midd.	L	-20	-86	-4	□	7.01
Cuneus (BA 18)	L	-2	-86	0	□	6.24
(BA17)	R	16	-82	6	48116 □	7.82

□indicates continuous voxels from cluster size: 48116

Region, anatomical region defined by MNI (Montreal Neurological Institute) coordinates in x, y, z, planes; H, hemisphere; L, left; R, right; Ant, Anterior; Sup, superior; Mid, Middle; Inf, Inferior; SMA, Supplementary Motor Area; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus; BA, Brodmann Area; MTG, Middle. Temporal Gyrus; STG, Superior Temporal Gyrus; ITG, Inferior Temporal Gyrus. Results at a significance threshold of $p < 0.05$ FDR corrected, with a 10-voxel cluster extent threshold.

Final conjunction analyses (one-way ANOVA) were conducted for the lexical-semantic task and the episodic retrieval task, separately, to identify *task-related* regions common to younger and older adults. *Figure 3.2, Table 3.2.C* and *Table 3.3.C* show the regions of overlap across age groups in each experimental task. The resulting contrast images confirmed the striking similarity of the placement of the successful task-related activations across the age groups previously described.

3.2.2. Brain activity associated with successful activity across tasks.

Two separate analyzes were conducted to order to determine regions involved successful activity across tasks for each group separately. First, to identify *task-general* or *shared* regions across tasks; and second, to identify *task-specific* activity by comparing activations between the two tasks.

Conjunction analyses were performed in each age group separately to identify *shared* regions elicited by both tasks while engaged in *task-general* activity (i.e., correct lexical-semantic judgments and hits in the episodic retrieval task). *Table* sections for the conjunction analyses results [*3.4.A.1* (young adults), *3.4.B.1* (older adults)] and *Figure 3.3* show the widespread activations in multiple posterior, frontal and parietal regions such as the middle frontal gyrus bilaterally, supplementary motor area, angular gyrus, and bilateral inferior and superior parietal lobules while performing both experimental tasks. In keeping with previous observations, the analysis shows that younger adults activations mirror the regions engaged by older adults, as well as that older adults showed greater bilateral brain activations than younger adults when performing both tasks (Cabeza et al., 2002; Park et al., 2010).
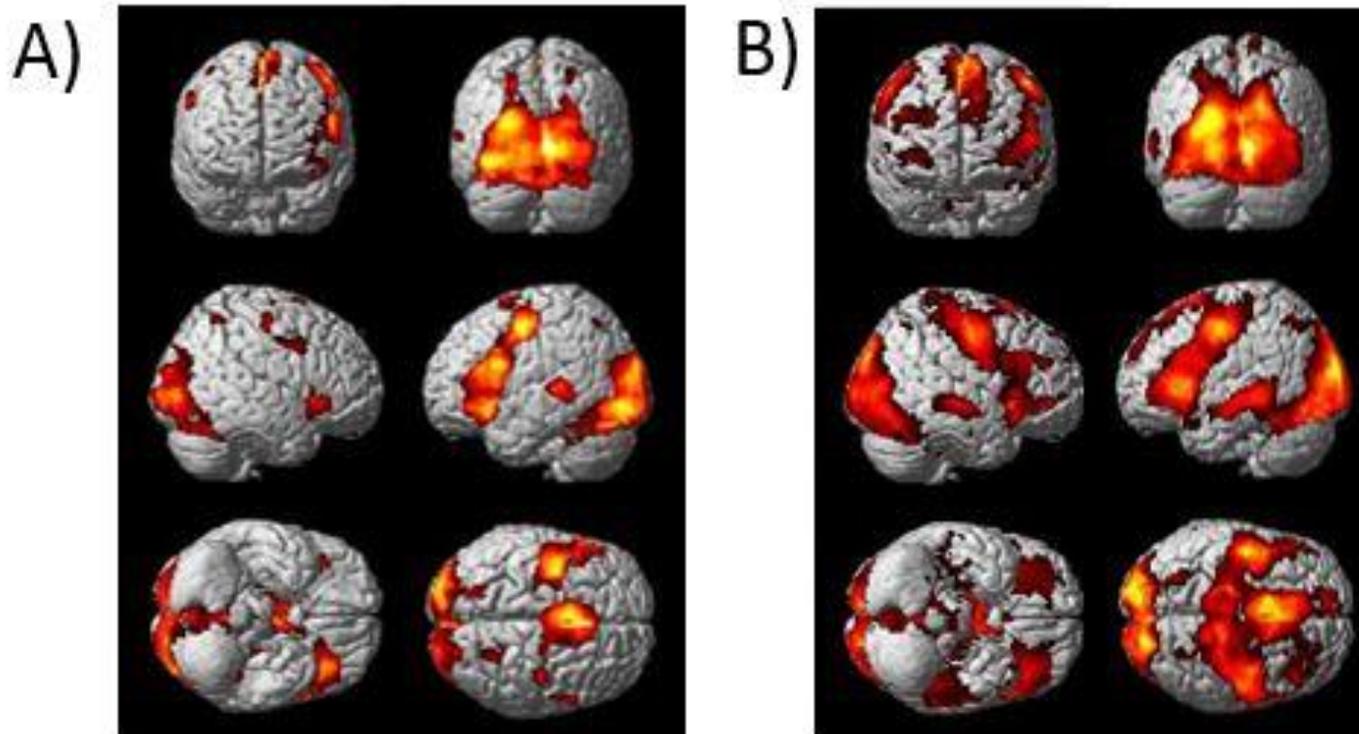
Figure 3.3. Patterns of *shared* brain activation for both tasks (*task-general*) in a conjunction analysis with each contrast image set to *p* < 0.05 FDR corrected, k=50, resulting in a joint probability of *p* < 0.0025, FDR corrected, for A) Younger Adults and B) Older Adults.

Table 3.4. Regions of whole brain activity in MNI coordinate space showing the patterns of activation for A) Younger Adults, B) Older Adults for 1) *task-general* (across both tasks and between tasks or *task-specific:* 2) Lexical-semantic task > Episodic retrieval memory task and 3) Episodic retrieval memory task > Lexical-semantic task.

Region	H	MNI Coordinate			Cluster Size (k)	*T*-value
		X	y	z		
A. Young Adults						
1. Task-general (Conjunction analysis)						
Sup. frontal gyrus includes SMA and BA 8	L/R	-4	14	54	35038	5.80
Sup. Temporal gyrus includes BA 22	L	-54	-32	4	503	4.05
Precuneus	R	26	-54	54	248	3.04
Precentral gyrus	R	40	-16	58	142	2.80
Inf. Frontal gyrus includes BA 9	R	58	8	40	127	3.40
Inf. Frontal gyrus	R	40	4	32	10	2.43
2. Task-specific: Lexical-semantic task > Episodic memory task						
Mid. Occipital gyrus	L	-46	-72	-2	68	4.46
3. Task-specific: Episodic memory task > Lexical-semantic task						
Inf. frontal gyrus	R	36	26	-6	54	4.52
B. Older Adults						
1. Task-general (Conjunction analysis)						
Occipital gyrus	L/R	-12	-80	-12	800084	7.72
Sup. frontal gyrus includes BA 10	R	26	62	14	29	2.89
Precentral gyrus	L	-64	-8	24	23	2.97
Med. frontal gyrus	L	-10	40	-10	10	2.28
2. Task-specific: Lexical-semantic task > Episodic memory task						
Occipital gyrus	L/R	10	-94	12	5553	5.42
Mid. temporal gyrus	L	-52	-42	-2	345	4.42
Putamen	L	-24	32	0	204	3.95
Mid. frontal gyrus includes BA 6	R	28	-8	52	139	3.92
Inf. temporal gyrus	R	44	-40	-8	70	3.53
Postcentral gyrus	R	12	-44	76	66	3.73
Precuneus	R	18	-50	46	51	3.59
3. Task-specific: Episodic memory task > Lexical-Semantic Task						
No Significant Clusters						

Region, anatomical region defined by MNI (Montreal Neurological Institute) coordinates in x, y, z, planes; H, hemisphere; L, left; R, right; Ant, Anterior; Sup, superior; Mid, Middle; Inf, Inferior; SMA, Supplementary Motor Area; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus; BA, Brodmann Area; MTG, Middle. Temporal Gyrus; STG, Superior Temporal Gyrus; ITG, Inferior Temporal Gyrus.

Regarding *task-specific* differences in functional activity across both tasks we used a one-sample T-Tests in each group separately to test for regions showing greater activation in *correct lexical-semantic judgments > hits in the episodic retrieval task* and the opposite contrast. These results were masked inclusively by the voxels identified on the conjunction analyses of each of the *task-general* activity conjunction maps of each age groups (see *Table 3.4.A.1* (young adults) and *3.4.B.1* (older adults)). As shown in *Figure 3.4,* younger adults showed greater activity in the left occipital gyrus for the lexical-semantic task greater than the episodic retrieval task contrast and right IFG for the episodic retrieval task greater than the lexical-semantic task.
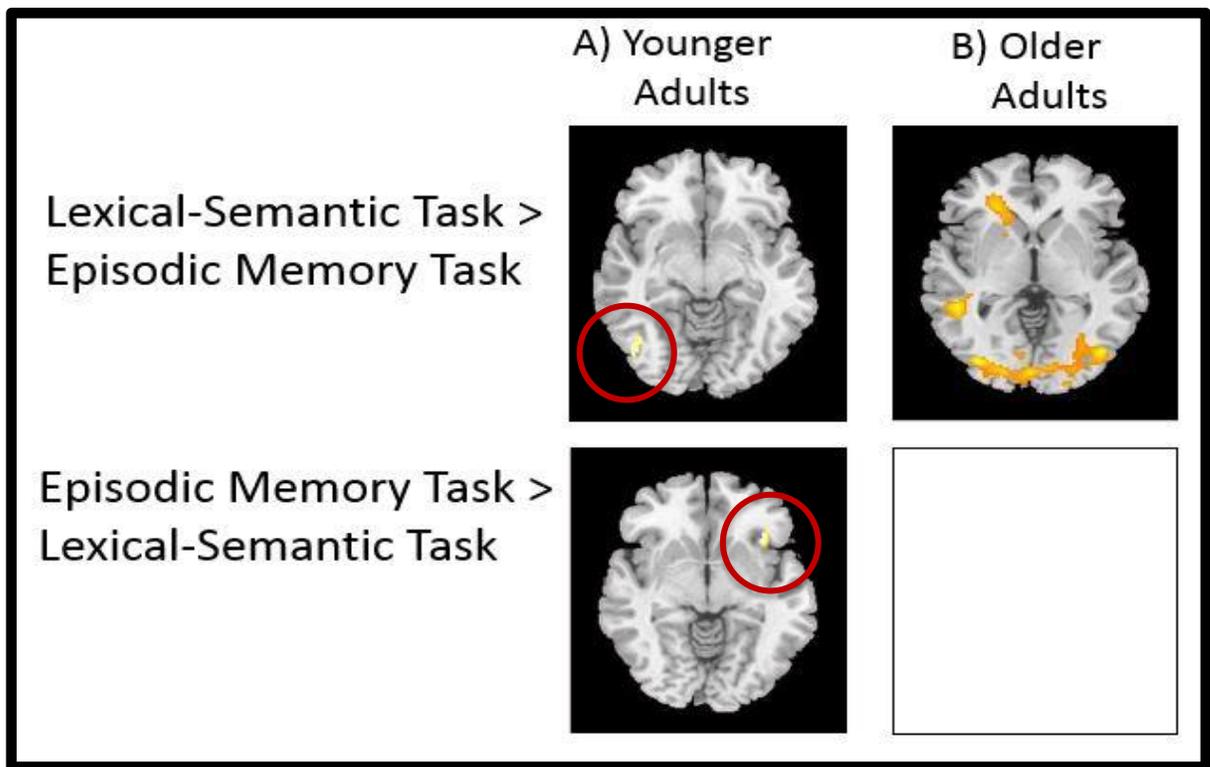
Figure 3.4. Transverse sections showing the location of the activations for the between task analyses (*task-specific*) for A) Younger Adults and B) Older Adults at a p<0.01, uncorrected.

While older adults did not show regions of greater activation when comparing accuracy in the episodic retrieval task greater than the lexical-semantic task, older adults showed multiple regions of greater activation in the lexical-semantic task greater than the episodic retrieval task (see *Table 3.4* and *Figure 3.4*). These regions included bilateral posterior regions, left middle temporal gyrus and putamen, and right temporal and parietal cortices including precuneus and inferior temporal gyrus.

3.2.3. Brain activity associated with increasing task difficulty.

Regions of activity that increased linearly as a function of increasing difficulty load are illustrated separately for the younger and older adults in *Figure 3.5* and section B of *Figure 3.6* (FDR corrected $p < 0.05$). Increases in difficulty were identified using the parametric modulation function with the coding ("1") for accurate trials in the Easy and ("2") for Difficult conditions. The results from the parametric linear modulation were masked inclusively by the voxels identified on the conjunction analyses of each of the *task-related* activity conjunction maps of both age groups (see *Figure 3.2* for a depiction of the inclusive masks and for region coordinates see sections of *Table 3.2.C.* (lexical-semantic task), *Table 3.3.C.* (episodic retrieval task).

In the lexical-semantic task, younger adults responded to increases in difficulty load by engaging bilateral occipital and frontal regions including the insula and IFG (triangular and operculum parts) regions. As difficulty increased, younger adults engaged extensive left hemisphere regions associated with verbal processing including the previously mentioned IFG orbital parts, as well as the middle frontal and lateral temporal cortices (both superior and middle temporal gyrus), replicating relevant aspects of the

basic left frontotemporal network regions associated with semantic processing

(Thompson-Schill et al, 1997; Rissman et al., 2003; Binder et al, 2009; Tyler et al.,

2010). In addition, as difficulty increased in the lexical-semantic task, young, but not

older, adults had increasing activation emerge in right cortices, i.e., the right

supplementary motor area (SMA) including BA 6, superior frontal, precentral gyrus,

cingulate gyrus and inferior parietal lobule. In contrast, older adults only responded to

increases in difficulty in the lexical-semantic task with increased activation in left-

lateralized areas of inferior frontal gyrus (operculum, triangular and orbital parts),

precentral gyus and posterior brain areas (See *Table 3.5* for region coordinates).

In contrast, older adults only responded to increases in difficulty in the lexical-

semantic task with increased activation in left-lateralized areas of inferior frontal gyrus

(operculum, triangular and orbital parts), precentral gyrus and posterior brain areas (See

Table 3.5 for region coordinates).

The most striking difference between the groups was that young adults exhibited

greater bilateral activations by engaging posterior and PFC regions as difficulty increased

in the lexical-semantic task, whereas older adults engaged only left hemisphere brain

regions. Yet, no group differences were observed within relevant semantic processing

regions such as in left IFG; in particular, Broca's area (defined as including triangular

and operculum parts, Foundas et al., 1998).

Table 3.6 shows the MNI coordinates and cluster extents for regions of activation

of linear increases in the episodic retrieval task. Younger adults showed increases in

bilateral posterior regions and subcortical regions, including the right cingulate cortex

and thalamus in response to increases in difficulty load. In contrast, for older adults,

greater increases in frontal activation were observed in medial and middle frontal gyrus, insula, cingulate gyrus and sensory-motor cortices including bilateral precentral and right postcentral gyrus. The distribution of activation in the older adults appeared to engage more medial and right-lateralized regions, including the frontal, parietal and temporal cortices. Overlapping regions of increasing activation in both groups were only observed in posterior regions, with younger adults engaging bilateral occipital regions, and older adults engaging right occipital lobe regions.
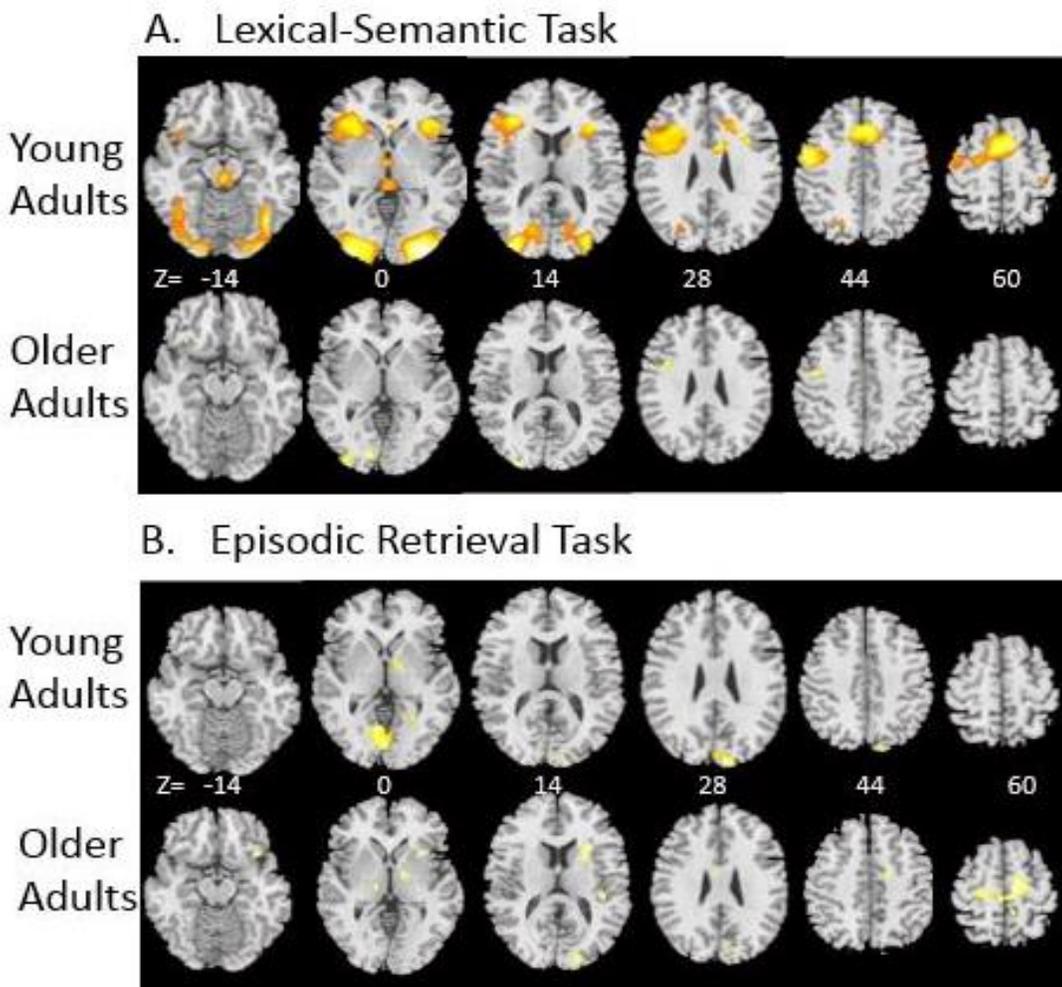

Figure 3.5. Regions of whole brain activity in MNI coordinate space showing the effects of the difficulty load manipulation (linear increases) in both experimental tasks for younger and older adults.

Table 3.5. Regions of whole brain activity in MNI coordinate space showing the effects of the difficulty load manipulation (linear increases) in the ***lexical-semantic task*** for A) younger and B) older adults.

Region	H	x	y	z	Cluster Size (k)	*T*-value
A. Young Adults						
Subcortical						
Caudate	R	14	6	20	*	4.94
Thalamus	L	-2	-28	-6	*	4.84
Cerebellum Ant. Lobe	L	0	-46	-36	42	4.03
Frontal						
Suppl. Motor Area (SMA) - includes BA 6	R	8	10	56	10571*	6.15
Middle Frontal Gyrus	L	-32	32	22	*	5.65
Insula	L	-30	22	2	*	4.78
(BA 13)	R	32	22	6	*	5.54
Cingulate Gyrus (BA 32)	R	6	20	46	*	5.19
Inf. Frontal Gyrus (IFG)	L	-40	4	34	*	4.87
- Triangular	L	-36	32	10	*	5.15
	R	28	16	26	*	3.68
- Orbital (BA47)	L	-32	30	-4	*	4.60
- Operculum	L	-46	12	8	*	3.20
	R	36	8	28	*	4.23
Precentral Gyrus (BA 4)	R	36	-26	56	84	3.65
	R	56	-6	40	11	2.81
Temporal						
Midd. Temporal Gyrus (MTG)	L	-60	-34	8	33▫	3.49
Sup. Temporal Pole	L	-48	14	-14	†	3.38
Sup. Temporal Gyrus (STG)	L	-66	-24	6	▫	2.87
Parietal						
Inferior Parietal Lobule (BA7)	R	28	-56	52	127	3.22

Region	H	x	y	z	Cluster Size (k)	*T*-value
Occipital						
Occipital Gyrus – Sup.	L	-22	-66	38	56	3.31
- Inferior	R	34	-92	-2	†	6.18
Occipital Gyrus - Midd., Sup.	L	-36	-92	14	3131	5.79
Calcarine Sulcus	R	14	-82	10	†	3.74

† indicates continuous voxels from cluster size: 2739; * indicates continuous voxels from cluster size: 10571; ▫ indicates continuous voxels from cluster size: 33

Region	H	x	y	z	Cluster Size (k)	*T*-value
B. Older Adults						
Frontal						
Inf. Frontal G (IFG)						
.-Triangular	L	-34	28	10	50	3.91
- Operculum	L	-40	6	18	185△	3.26
- Orbital	L	-34	22	-10	33	2.87
- Triangular	L	-52	30	4	19	2.68
Precentral Gyrus (BA 6)	L	-44	-6	40	△	3.49
Occipital						
Lingual Gyrus	L	-14	-86	0	57	3.73
Middle Occipital Gyrus	L	-30	-98	10	177	3.29

△ Indicates continuous voxels from cluster size: 185

Region, anatomical region defined by MNI (Montreal Neurological Institute) coordinates in x, y, z, planes; H, hemisphere; L, left; R, right; Ant, Anterior; Sup, superior; Mid, Middle; Inf, Inferior; SMA, Supplementary Motor Area; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus; BA, Brodmann Area; MTG, Middle. Temporal Gyrus; STG, Superior Temporal Gyrus; ITG, Inferior Temporal Gyrus.

Table 3.6. Regions of whole brain activity in MNI coordinate space showing the effects of the difficulty load manipulation (linear increases) in the ***episodic retrieval task*** for A) younger and B) older adults.

Region	H	MNI Coordinate x	Y	Z	Cluster Size (k)	*T-*value
1. Young Adults						
Subcortical						
Thalamus	R	12	-4	0	29	3.31
Frontal						
Cingulate Cortex	R	20	-10	40	15	3.03
Occipital						
Cuneus (BA 19)	L	-2	-82	32	†	3.10
	R	7	-87	39	358†	4.31
Lingual Gyrus (BA 18)	L	-8	-64	0	684△	3.87
	R	6	-70	2	△	2.64

† indicates continuous voxels from cluster size: 358; △ indicates continuous voxels from cluster size: 684

Region	H	MNI Coordinate x	Y	Z	Cluster Size (k)	*T-*value
2. Older Adults						
Subcortical						
Putamen	R	26	14	10	299∞	3.22
Thalamus	L	-16	-20	4	38	2.76
	R	16	-6	2	98	2.74
Frontal						
Middle Frontal Gyrus	R	14	-12	66	789*	3.30
Insula (BA13)	R	32	16	-6	∞	3.10
Cingulate Cortex (BA 32)	L/R	-4	10	40	33	2.80
Medial Frontal Gyrus	L/R	-6	-26	58	*	2.83
Precentral Gyrus (BA 6)	L/R	-20	-20	64	149	2.84
	R	52	-12	44	93	2.78
Postcentral Gyrus	R	21	-37	71	20	2.72
Temporal						
Sup. Temporal Gyrus (STG)	R	44	-30	12	53	3.22
Parietal						
Precuneus	R	8	-88	38	156‡	3.37
Paracentral Lobule	R	8	-42	62	49	2.87
Occipital						
Cuneus	R	25	-84	26	∞	2.58
Sup. Occipital Gyrus	R	20	-100	18	61	3.19
Lingual Gyrus	R	4	-70	-4	15	2.76

* indicates continuous voxels from cluster size: 789; ‡ indicates continuous voxels from cluster size: 156; ∞ indicates continuous voxels from cluster size: 299.

Region, anatomical region defined by MNI (Montreal Neurological Institute) coordinates in x, y, z, planes; H, hemisphere; L, left; R, right; L/R, medial. Ant, Anterior; Sup, superior; Mid, Middle; Inf, Inferior; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus; BA, Brodmann Area; STG, Superior Temporal Gyrus.
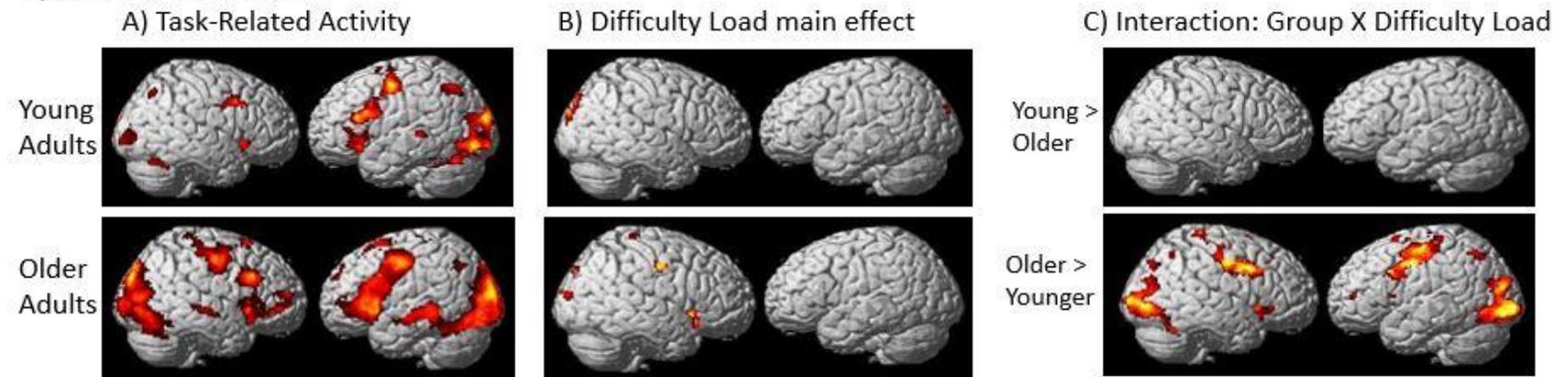
61
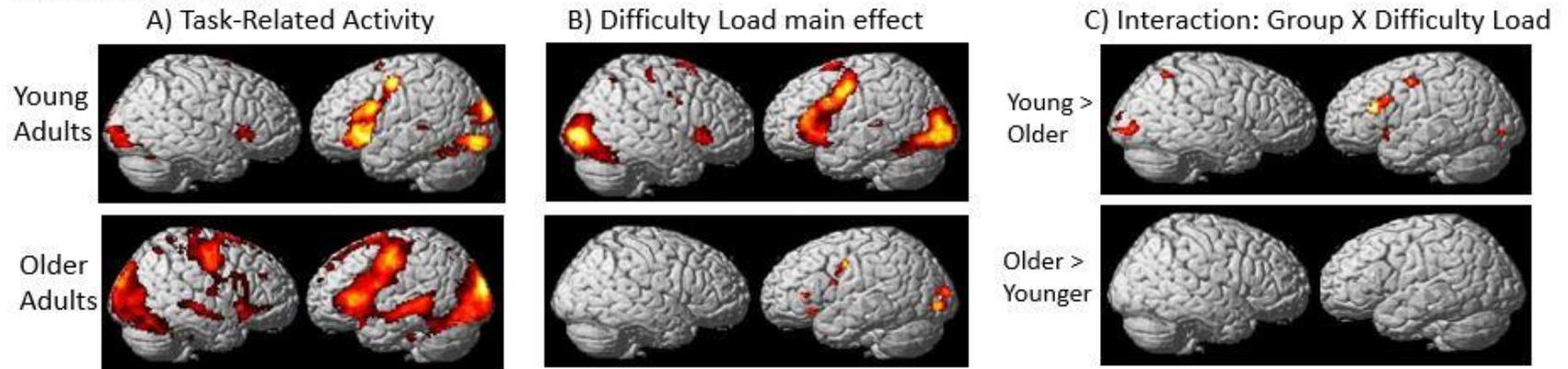
Figure 3.6. Regions engaged during the lexical-semantic task (Top) and episodic retrieval task (bottom) A) task-related activity, B) the effect of difficulty and C) Group by difficulty load interaction.

3.2.4. Age effects differences on the fMRI activation as a function of Difficulty Task increases.

We next examined age group differences in the linear increases due to difficulty load by contrasting the two age groups across the linear increases parametric model in which we investigated the main effect of the difficulty load manipulation. *Figure 3.6.C* and *Table 3.7* show the interaction effects of group by increasing difficulty load in each task separately.

In the lexical-semantic task as difficulty load increased, compared to older adults, younger adults continued to engage the previously described left-lateralized frontal activations associated with semantic processing. Younger adults also showed larger increases in medial PFC including SMA, midbrain regions, bilateral occipital and right superior parietal lobule compared to older adults (*Figure 3.7.A*). Furthermore, in line with our expectation that the lexical-semantic task was not difficult for the older adults, no significant regions of greater increase emerged for older adults compared to young adults.

On the other hand, the age group comparison across the difficulty load in the episodic retrieval task showed that older adults exhibit greater increases in activation in bilateral frontal and parietal regions compared to younger adults (*Figure 3.7.B*). The reverse comparison did not elicit any significant differences between younger and older adults – young adults did not show greater difficulty-related increases in any region compared to older adults.
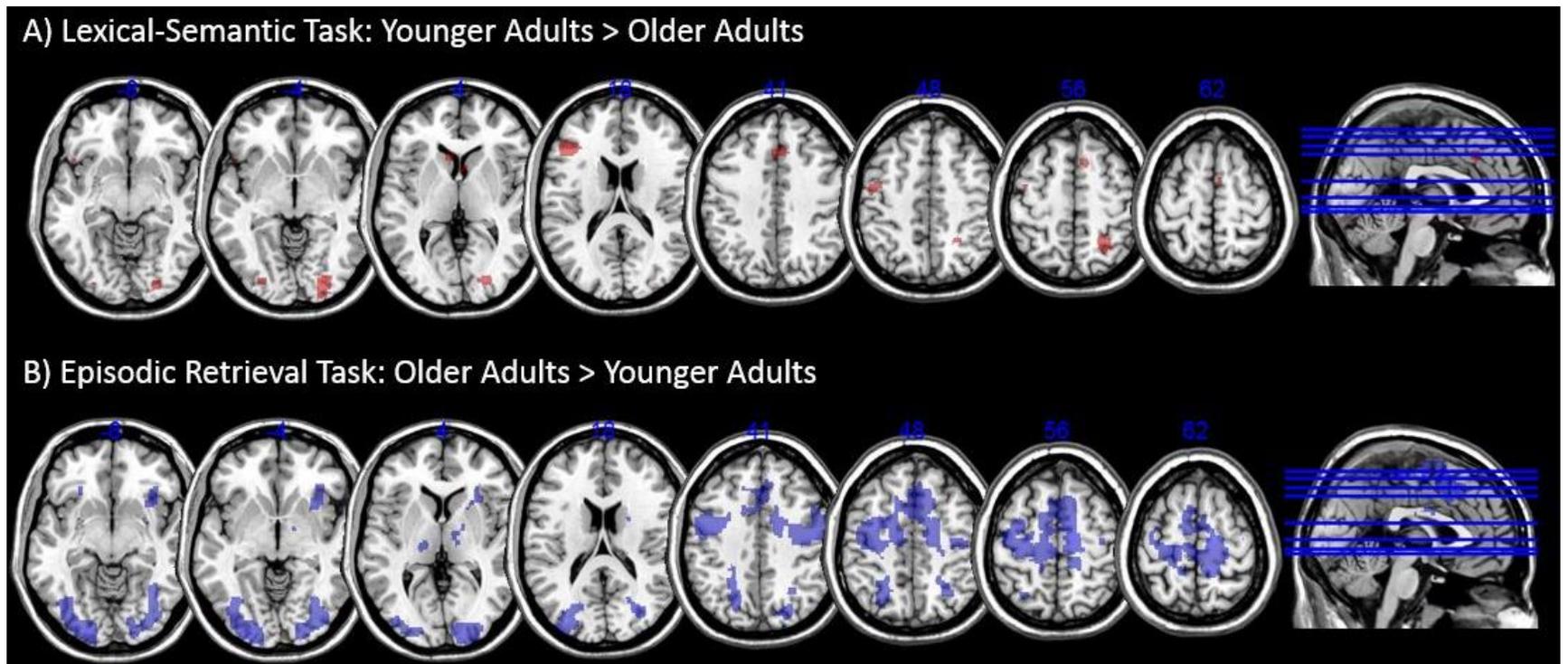
Figure 3.7. Between group effects in A) lexical-semantic task; Red: younger adults>older adults and B) episodic retrieval task; Blue: older adults > younger adults. All results are displayed at a threshold of p<0.01 with a 10-voxel cluster extent on an axial slices of a single brain spatially normalized to MNI space.

Table 3.7. Regions showing the **interaction** effect by showing between Groups contrasts (1) Young > Older and (2), Older > Young in MNI coordinate space as <u>difficulty load increased</u> in the A) lexical-semantic task and in the B) episodic retrieval task.

Region	H	MNI Coordinate			Cluster Size (k)	*T*-value
		X	y	Z		
A. lexical-semantic task						
1. Young Adults > Older Adults						
Subcortical						
Caudate	L	-8	20	8	59	3.93
	R	12	10	24	54	3.49
Frontal						
Inf. Frontal Gyrus (IFG) - BA 46	L	-48	28	20	450	3.59
- Triangular	L	-50	16	-2	28	2.56
Sup. Frontal Gyrus/SMA	L/R	10	16	54	48	2.77
Sup. Frontal Gyrus/SMA	L/R	6	-2	62	10	2.60
Cingulate Cortex (BA 32)	L/R	4	28	34	169	3.26
Postcentral Gyrus - BA 6	L	-50	-8	48	110	3.11
Parietal						
Sup. Parietal Lobule	R	-56	56	26	171	3.42
Occipital						
Occipital Gyrus - Inf.	L	-28	-86	-6	26	2.72
-Midd. (BA19)	R	30	-98	10	21	3.14
2. Older Adults > Younger						
No Significant Clusters						
B. Episodic retrieval task						
1. Young Adults > Older Adults						
No Significant Clusters						
2. Older Adults > Younger Adults						
Subcortical						
Putamen	R	24	10	8	582∞	3.45
Frontal						
Insula (BA13)	R	34	18	-8	∞	3.33
Inf. Frontal Gyrus (IFG) –Triangular	R	30	32	2	∞	2.64
Middle Frontal Gyrus -BA 10	L	-34	48	10	21	2.81
Middle Frontal Gyrus/SMA	L/R	14	-12	66	8791	4.01
Cingulate Cortex	R	12	2	38	57	2.98

Table 3.7 Continued…

Region		MNI Coordinate			Cluster Size (k)	*T*-value
		X	y	Z		
Temporal						
Sup. Temporal Gyrus (STG)	R	42	-30	14	31	2.75
Parietal						
Paracentral	R	10	42	62	△	3.05
Occipital						
Occipital G.-Inf., Midd.	L	-24	-94	-6	2397	3.34
Calcarine sulcus	R	18	-96	4	2547△	3.21

∞ indicates continuous voxels from cluster size: 582; △ indicates continuous voxels from cluster size: 2547

Region, anatomical region defined by MNI (Montreal Neurological Institute) coordinates in x, y, z, planes; H, hemisphere; L, left; R, right; Ant, Anterior; Sup, superior; Mid, Middle; Inf, Inferior; SMA, Supplementary Motor Area; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus ;BA, Brodmann Area; MTG, Middle. Temporal Gyrus; STG, Superior Temporal Gyrus; ITG, Inferior Temporal Gyrus. Results at a significance threshold of p<0.01 uncorrected, with a 10-voxel cluster extent threshold.

Follow-up ROI analyses were carried out to determine the nature of the group by difficulty load interactions for each task separately. To generate the ROIs, we isolated the local maxima in a region based on the interactions and then drew a 5 mm diameter sphere around those voxels. We extracted mean parameter estimates (beta weights) for contrasts of interests in each task separately for young and older participants to each individual's contrast images from the corresponding first-level analyses and parameter estimates were extracted for statistical analyses (i.e., lexical-semantic correct judgments Easy Condition> Controls in the lexical-semantic task). Parameter estimates extracted as a function of age are shown in *Figure 3.9* for the lexical-semantic task and in *Figure 3.9* for the episodic retrieval task.
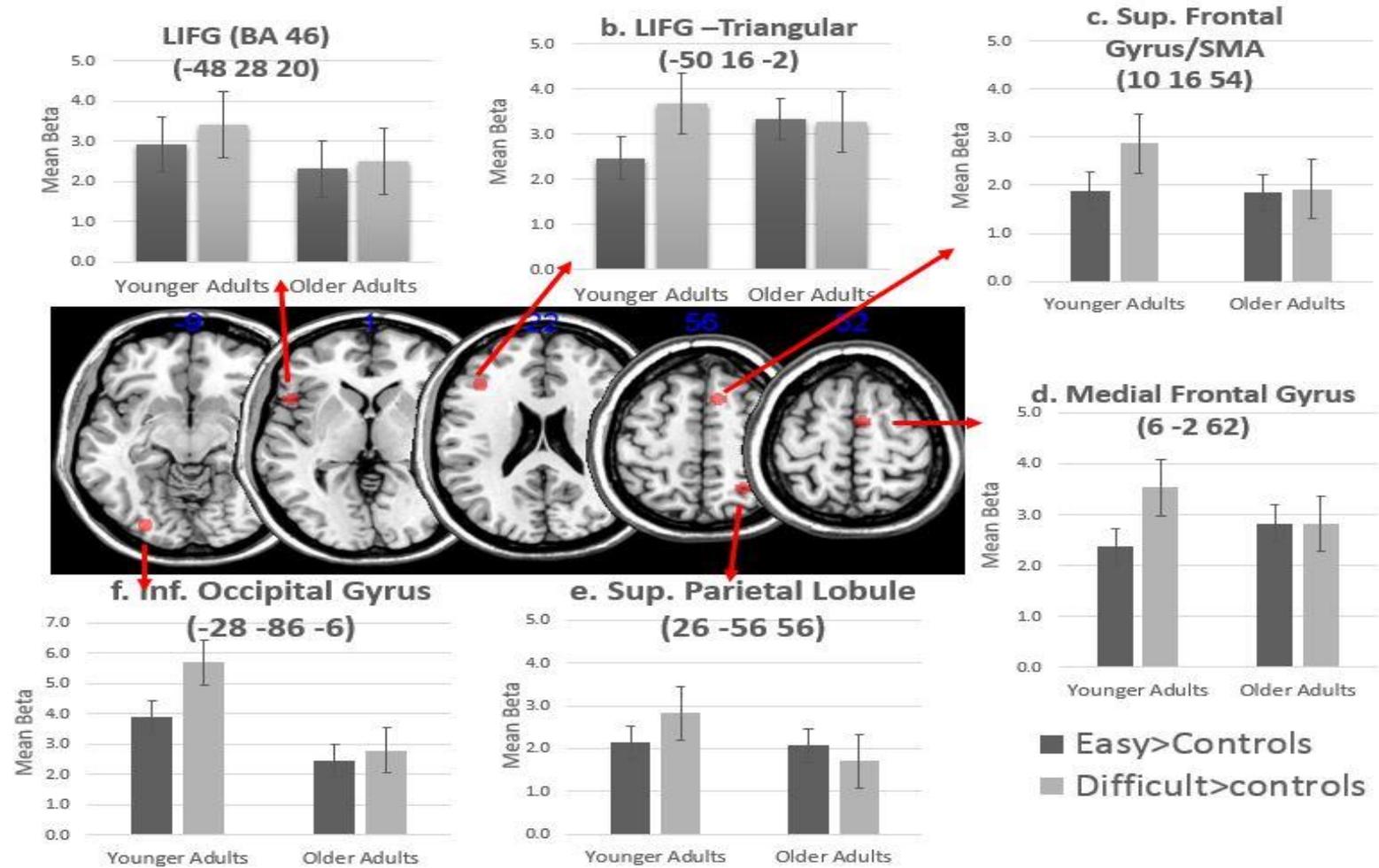
Figure 3.8. ROIs for the interaction difficulty load by age in the lexical-semantic task.
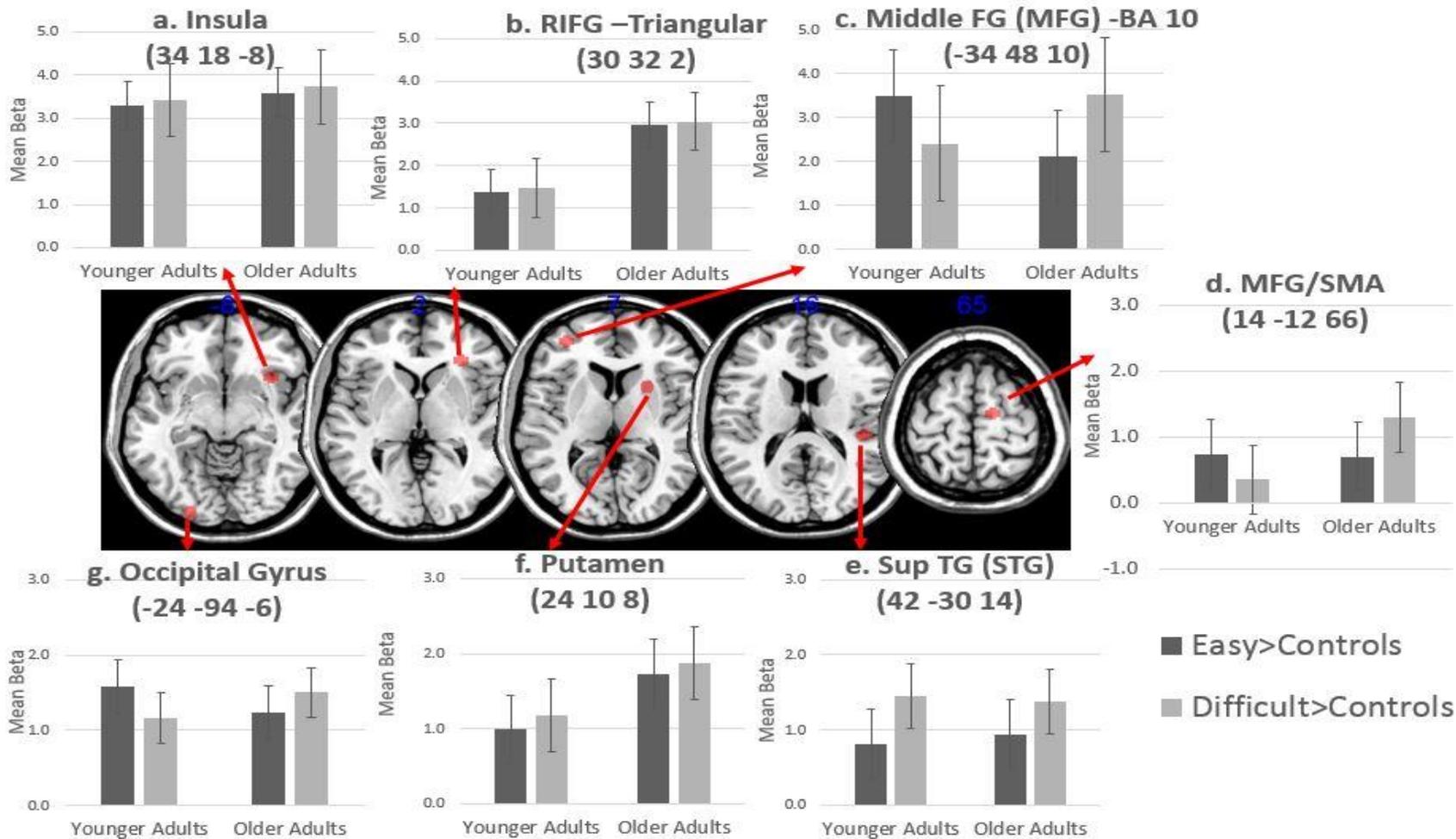
Figure 3.9. ROIs for the interaction difficulty load by age in the episodic retrieval task.

We assessed the effects of age and difficulty on activations in the ROIs with a 2 x 5 x 2 (lexical-semantic task) or 2 x 5 x 2 (episodic retrieval task) mixed factor GLM. Age group was entered as the between-subjects factor, 5 (*Figure 3.8.* A through E) or 6 (*Figure 3.9.* A through E)[5] for the number of ROIs as a repeated measure, and Difficulty Load (Easy, Difficult) as the within-subjects factor. In the lexical-semantic task or the episodic retrieval task, the activations between younger and older adults did not differ, $F < 1$, n.s. Also, all main effects or interaction not reach significance, $F < 1$, n.s.

3.2.5. Behavior- fMRI Correlations.

We examined how activity affected performance in the regions showing a group by difficulty interaction in the ROIs from *Table 3.7*, including the ones depicted in *Figure 3.8* and *3.9*. Correlations between the extracted beta weights from each ROI and their respective accuracy scores were calculated separately between activity in either Easy > Control or Difficult > Control conditions performance (i.e., lexical semantic task: percent of correct judgments and in the episodic retrieval task: D Prime). The correlations (see *Table* 3.8 for results) were conducted to further examine whether the observed increases in activation in either of the tasks were related to task performance.

In the lexical-semantic task, both groups showed a negative correlation between performance in the Easy condition and ROI beta weights from the superior fontal gyrus/SMA (MNI: Left -34, 48, 10) indicating that as performance in the Easy pairs of lexical-semantic task increased activation decreased. Younger adults also showed a

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[5] Note that the occipital gyri ROI for both tasks were not included in the analyzes since no apriority hypothesis were made concerning this area as being relevant in either task.

negative correlation trending toward significance between percent correct judgments and

beta weights for the cingulate gyrus (MNI: Right, -4 -28 34; light gray highlight in *Table 3.8*) during the Easy condition in the lexical-semantic task.

Table 3.8. Person Correlations between accuracy and fMRI Beta weights.

	Region	Easy		Difficult	
		Younger	Older	Younger	Older
		r	r	r	r
Figure 6	**Lexical-Semantic Task (Accuracy)**				
a.	Left IFG - BA 46	-0.01	0.15	-0.08	-0.13
b.	Left IFG - Triangular	-0.02	0.26	-0.28	0.02
c.	Sup. Frontal Gyrus/SMA	**-0.41***	**-0.42***	0.14	0.17
d.	Medial FG	-0.18	-0.01	0.06	0.09
e.	Right Sup. Parietal Lobule	-0.19	0.002	0.13	0.22
f.	Left Occipital Gyrus	-0.05	-0.12	0.18	0.19
	Right Cingulate Cortex	*-0.35‡*	0.04	-0.12	0.18
	Postcentral Gyrus - BA 6	-0.13	-0.07	-0.17	0.13
Figure 7	**Episodic Retrieval Task (Accuracy: D Prime)**				
a.	Right Insula	-0.16	0.19	-0.14	-0.11
b.	Right IFG –Triangular	0.21	0.07	0.09	0.06
c.	Left Mid. FG -BA 10	-0.15	0.23	-0.005	0.07
d.	Mid. FG/SMA	-0.24	0.29	-0.05	*0.379∞*
e.	Right STG	-0.11	0.03	0.13	-0.01
f.	Putamen	-0.05	0.17	-0.15	-0.03
g.	Left Occipital Gyrus	-0.18	0.33	0.14	0.273
	Left Cingulate Cortex	-0.05	-0.01	0.22	-0.17
	Right Paracentral	0.16	0.193	0.12	0.001

* p<0.05   ‡ *p = 0.087*   ∞ *p=0.068*

Region, anatomical region defined by MNI (Montreal Neurological Institute); BA, Brodmann Area; Sup, superior; Mid, Middle; Inf, Inferior; FG, Frontal Gyrus; SMA, Supplementary Motor Area; IFG, Inferior Frontal Gyrus; MTG, Middle. Temporal Gyrus; STG, Superior Temporal Gyrus.

There were no significant correlations of BOLD beta weights with accuracy in the

younger or older adults for the episodic retrieval task, although older adults showed some

trends within Medial Frontal Gyrus /SMA (MNI: Right, 14, -12, 66) and D' prime scores (light gray highlight in *Table 3.8*).

Finally, correlations between the extracted beta weights from each ROI and their RT were calculated separately between activity in either Easy > Control or Difficult > Control conditions performance in the lexical semantic task only. The correlations (see *Table* 3.9 for results) indicated that increases in activation was related to RT for younger adults in the Easy condition in two regions. First the right cingulate cortex (MNI: Right, - 4 -28 34) and the postcentral gyrus (MNI: Left, -50 -8 -48), both with a positive correlation, suggesting that as activations in these regions increased, younger adults performed slower at judging the lexical-semantic pairs. Younger adults also showed a negative correlation trending toward significance for the superior fontal gyrus/SMA (MNI: Right, 10 16 54; light gray highlight in *Table 3.9*). Taken together with the aforementioned negative correlation between performance in the Easy condition and ROI beta weights from the superior fontal gyrus/SMA and posterior cingulate, it is suggested that for younger adults in the Easy condition, activity in those regions is associated with better performance and slower response times.

Older adults showed a positive correlation between RT in the Difficult condition and the BOLD beta weights from the right superior parietal lobule (MNI: Right, 28 -56 52), indicating that increased activation in this region was associated with slower performance. However, older adults also showed three negative correlation trending toward significance between RT in the Difficult condition and the ROI activity: the superior fontal gyrus/SMA (MNI: Right, 10 16 54), Occipital Gyrus (MNI: Left, -28 -86 - 6), and inferior frontal –triangular parts (MNI: Left, -50 16 -2; light gray highlight in

Table 3.9) indicating that faster RTs in these regions was associated with increased

activations.

Table 3.9. Person Correlations between Reaction Times (RT) and fMRI Beta weights.

	Region	Easy		Difficult	
		Younger	Older	Younger	Older
		r	r	r	r
Figure 6	**Lexical-Semantic Task**				
a.	Left IFG - BA 46	0.21	0.07	0.17	0.16
b.	Left IFG - Triangular	0.27	-0.13	0.33	-0.36∞
c.	Sup. Frontal Gyrus/SMA	*0.39‡*	0.03	-0.13	-0.38†
d.	Medial FG	0.06	-0.07	0.08	-0.28
e.	Right Sup. Parietal Lobule	0.27	-0.18	-0.09	**0.44***
f.	Left Occipital Gyrus	0.17	-0.22	0.03	-0.39†
	Right Cingulate Cortex	**0.47***	0.03	0.30	-0.21
	Postcentral Gyrus - BA 6	**0.48***	0.03	0.15	-0.06

* p<0.05   *‡ p = 0.058*   *∞ p = 0.082*   *† p= 0.055*
Region, anatomical region defined by MNI (Montreal Neurological Institute); BA,
Brodmann Area; Sup, superior; Mid, Middle; Inf, Inferior; FG, Frontal Gyrus; SMA,
Supplementary Motor Area; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus;
MTG, Middle. Temporal Gyrus; STG, Superior Temporal Gyrus

3.2.6. Complementary Analyses.

Given that we could not find reliable correlations between the BOLD beta weights

and performance in either task to support the compensatory response account, we divided

each group based on a median split of their neuropsychological scores, a common

strategy used to investigate the compensatory response (Cabeza et al, 2002; Rosen et al.,

2002; Angel et al., 2016). The younger adult group was divided based on their North

American Adult Reading Test (NAART) scores into high performers (mean ± SD = 52.00

± 4.32) and low performers (mean ± SD = 38.12 ± 4.06). The older adult group was

divided using a median split based on an executive function score thought to represent

executive function (Frontal) scores into high performers (mean ± SD = 0.53 ± 0.46) and low performers (mean ± SD = -0.59 ± 0.34; see Glisky et al., 1995; Glisky et al., 2001; Glisky & Kong, 2008 for details).

Lexical-semantic task.

We were interested to determine whether the observed results in the lexical-semantic task were due because variability in vocabulary knowledge, first among the younger adults, and second, by comparing the overall older adults group with the high-performing younger adults. The following results were masked inclusively by the voxels identified on the conjunction analyses of the lexical-semantic task see *Figure 3.2* for a depiction of the inclusive masks and for region coordinates see section C of *Table 3.2* (lexical-semantic task). First, we were interested in identifying the regions engaged by the each of the two subgroups of younger adults as difficulty increased in the lexical-semantic task. While the low performers did not show regions of activation at *p* < .001, uncorrected, k=10, the high performers showed multiple regions, particularly replicating the results of the overall younger adults group (see *Table 3.10 and Figure 3.10.A*). These regions included bilateral inferior frontal, parietal, occipital and subcortical regions. Additional regions included left middle and superior frontal gyrus, cingulate gyrus, superior temporal and precentral gyrus.

Table 3.10. Location of regions of greater activation as difficulty increased in the lexical semantic task for *high- performing* younger adults.

Region	H	MNI Coordinate			Cluster Size (k)	*T*-value
		x	y	Z		
Subcortical						
Caudate	R	14	14	-4	*	4.70
Thalamus	L	0	-16	8	112	5.11
Frontal						
Suppl. Motor Area (SMA)	R	6	16	64	‡	5.92
Middle Frontal Gyrus (BA 6)	L	-54	2	42	116∞	4.76
Cingulate Gyrus	L	-12	24	32	15	3.72
Inf. Frontal Gyrus (IFG)	R	38	24	-4	577*	7.31
- Triangular	L	-34	32	2	646	4.01
- Triangular (BA 45)	L	-50	20	14	487	499
Superior Frontal Gyrus	R	8	14	54	519‡	6.83
Precentral Gyrus (BA 9)	L	-40	2	32	∞	4.72
Temporal						
Sup. Temporal Gyrus (STG)	L	-48	16	-20	25	6.98
Parietal						
Precuneus	L	-24	-64	38	11	5.29
Sup. Parietal Lobule	R	30	-58	54	36	4.76
Occipital						
Midd. Occipital Gyrus	L	-30	-82	2	1235	6.04
Inf. Occipital Gyrus	R	34	-90	-6	1380	4.10

* indicates continuous voxels from cluster size: 577. ‡ indicates continuous voxels from cluster size: 519. ∞ indicates continuous voxels from cluster size: 116.

Region, anatomical region defined by MNI (Montreal Neurological Institute) coordinates in x, y, z, planes; H, hemisphere; L, left; R, right; Ant, Anterior; Sup, superior; Mid, Middle; Inf, Inferior; SMA, Supplementary Motor Area; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus; BA, Brodmann Area; MTG, Middle. Temporal Gyrus; STG, Superior Temporal Gyrus; ITG, Inferior Temporal Gyrus.
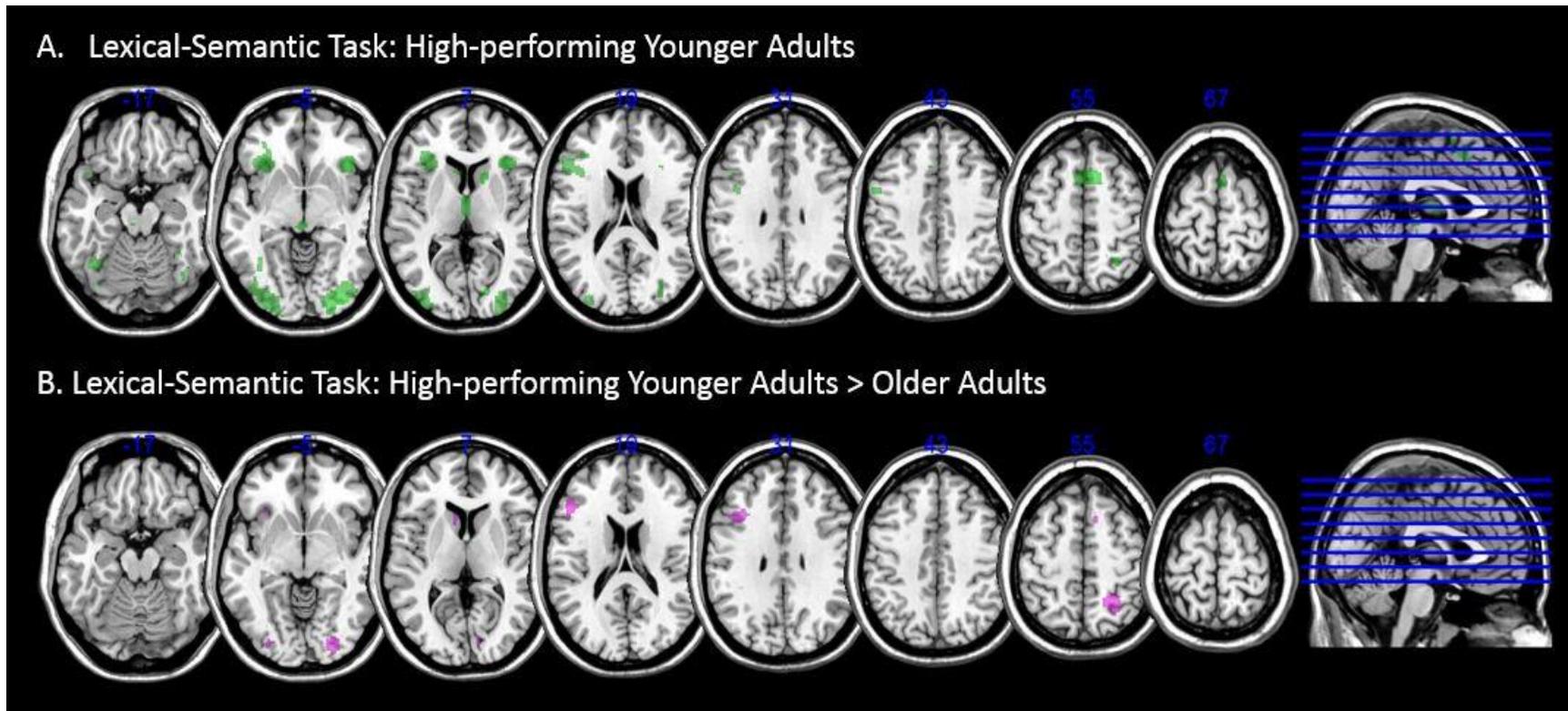
Figure 3.10. Patterns of brain activation as Difficulty Load increased in A) high-performing younger adults (n=12) and the age group differences analyses B) high-performing younger adults greater than older adults (n=24).

We also compared the higher functioning young adults to the older adults. Independent samples *t*-tests were performed in order to determine regions whether the twelve young high performers showed greater activation than the entire sample of older adults across the linear increases in the lexical-semantic task. As shown in *Figure 3.10.B* and *Table 3.11*, we observed activations in left inferior frontal gyrus, middle frontal gyrus, caudate, right superior frontal gyrus and precuneus, and bilateral occipital regions. The opposite contrast comparing older adults greater than young high performers did not show regions of significant activation at a threshold of $p < .001$, uncorrected, k=10.

Table 3.11. Location of regions showing the comparison of *high-performing* younger adults compared to older adults as difficulty increased in the lexical semantic task.

Region	H	MNI Coordinate x	Y	Z	Cluster Size (k)	*T*-value
Subcortical						
Caudate	L	-10	18	8	14	3.78
Frontal						
Inf. Frontal Gyrus (IFG) - BA 45	L	-48	26	18	339†	4.47
- Triangular	L	-38	20	28	†	3.67
- BA 47 and insula	L	-34	22	-6	10	3.35
Midd. Frontal Gyrus /precentral gyrus	L	-44	-4	52	16	3.64
Sup. Frontal Gyrus/SMA	R	10	16	54	13	3.55
Parietal						
Precuneus (BA 7)	R	28	-56	54	221	4.88
Occipital						
Occipital Gyrus	L	-30	-86	-6	17	3.64
	R	24	-86	-4	186	4.90

† indicates continuous voxels from cluster size: 339.

Region, anatomical region defined by MNI (Montreal Neurological Institute) coordinates in x, y, z, planes; H, hemisphere; L, left; R, right; Ant, Anterior; Sup, superior; Mid, Middle; Inf, Inferior; SMA, Supplementary Motor Area; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus; BA, Brodmann Area; MTG, Middle. Temporal Gyrus; STG, Superior Temporal Gyrus; ITG, Inferior Temporal Gyrus.

Episodic retrieval task.

We aimed to determine individual differences in high- and low- performing older adults in performing the episodic retrieval task. As with the previous complementary analyses in the lexical semantic task, by inclusively masking the voxels identified on the conjunction analyses of the episodic retrieval task (see *Figure 3.2* for a depiction of the inclusive masks and for region coordinates see section C of *Table 3.3)* we identified regions engaged by *high-performing older adults*. These regions were located in the right hemisphere including the inferior frontal gyrus extending to the insula, superior temporal gyrus and putamen (see *Table 3.12*). Similar to the results for the younger adults in the lexical-semantic task, the low-performing group of older adults did not show regions of significant activation in the episodic retrieval task (see *Figure 3.11.A*).
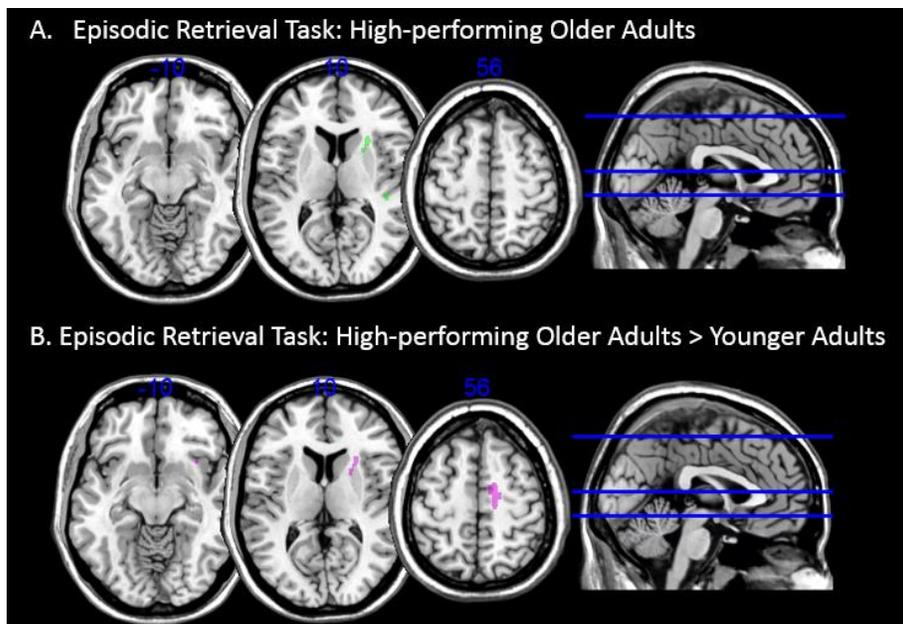

Figure 3.11. Patterns of brain activation as Difficulty Load increased in A) high-performing older adults (n=12) and the age group differences analyses B) high-performing older adults greater than younger adults (n=24).

Table 3.12. Location of regions of greater activation as difficulty increased in the episodic retrieval task for *high-performing* older adults.

Region	H	MNI Coordinate x	Y	z	Cluster Size (k)	*T*-value
Subcortical						
Putamen	R	26	16	12	51	3.09
Frontal						
Inf. Frontal Gyrus (IFG) – Insula	R	30	14	-2	29	2.99
Temporal						
Sup. Temporal Gyrus (STG)	R	42	-28	8	13	3.14

Region, anatomical region defined by MNI (Montreal Neurological Institute) coordinates in x, y, z, planes; H, hemisphere; L, left; R, right; Sup, superior; Inf, Inferior; IFG, Inferior Frontal Gyrus; SFG, Superior Frontal Gyrus; STG, Superior Temporal Gyrus.

Table 3.13. Location of regions showing the comparison of *high-performing* older adults compared to younger adults as difficulty increased in the episodic retrieval task.

Region	H	MNI Coordinate x	Y	Z	Cluster Size (k)	*T*-value
Subcortical						
Putamen	R	26	16	12	51	3.80
Frontal						
Inf. Frontal Gyrus (IFG) - Insula	R	34	16	-8	22	3.23
Mid. Frontal Gyrus	R	16	-12	64	222△	4.26
Parietal						
Postcentral Gyrus	R	12	-32	74	△	3.69
△ indicates continuous voxels from cluster size: 222.						

Region, anatomical region defined by MNI (Montreal Neurological Institute) coordinates in x, y, z, planes; H, hemisphere; L, left; R, right; Mid, Middle; Inf, Inferior; IFG, Inferior Frontal Gyrus.

Differences in activation between younger and the *high-performing* older adults were also examined using an independent samples *t*-tests across the linear increases in the episodic retrieval task. While younger adults did not show regions of greater activation than high-performing older adults, high-performing older adults showed multiple regions of greater activation than younger adults, particularly in the right hemisphere including the putamen, middle and inferior frontal gyrus (see *Figure 3.11.A* and *Table 3.13*).

CHAPTER 4

DISCUSSION

The present study investigated age-related differences in fMRI activation in two tasks –lexical-semantic and episodic retrieval– that were expected to be differentially harder for younger and older adults, with difficulty manipulated in both tasks by varying word frequency. Our experimental design allowed us to compare two identical tasks in every respect except for the type of memory judgment made by the participants to understand age effects on how brain activation is modulated by difficulty load. The behavioral data showed a double dissociation where older adults outperformed the younger adults on the lexical-semantic task as difficulty increased. In contrast, younger adults were not affected as older adults by difficulty increases in the episodic retrieval task. fMRI results showed both groups engaged similar brain regions in both experimental tasks when eliciting *task-related* activity regardless of difficulty. The same pattern was observed for both groups while performing both experimental tasks (i.e., *task-general* activity). Age-related differences were observed for *task-specific* and linear increases due to difficulty. Most importantly, difficulty load increases paralleled the groups' behavioral results: younger adults showed greater increases in activity in the lexical-semantic task compared to older adults, but not in the episodic retrieval task, whereas older adults showed the opposite pattern, with greater increases in activation only in the episodic task when compared to younger adults. Finally, relying on correlation analyses, we did not observe a relationship between BOLD signal estimates and performance on either task, for either age group. The main behavioral and functional imaging findings from this study are summarized and fully discussed below.

Behavioral Performance.

As expected, behavioral data indicated younger adults and older adults showed a double dissociation in behavioral performance in two tasks that were hypothesized to be differentially more challenging for the two groups studied. Older adults were adversely affected in the episodic memory retrieval task with increasing task difficulty. In contrast, in the lexical-semantic task, younger adults were more adversely affected by increasing difficulty than the older adults. Our behavioral results are consistent with Kavé and Yafé (2014) showing that younger adults outperformed older adults on tests of episodic retrieval, whereas older adults outperformed younger adults on tests of lexical-semantic memory (vocabulary: giving definition of words in several modalities). Also, our behavioral results corroborate previous observations from cross-sectional studies such as Rönnlund at el. (2005) comparing multiple cognitive domains including semantic and episodic memory across adults ranging in age from 35-80 years (see also Park et al., 2002), where adults do not show age-related declines in lexical-semantic tasks (i.e., world knowledge, vocabulary) as compared to other measures that show age-related declines including episodic memory, speed of processing, and working memory.

The present results also showed that the high and low word frequency words were able to differentially determine the two experimental tasks types studied, supporting the word-frequency effect (WFE; Glanzer & Adams, 1985). In lexical-semantic task with predicted accuracy and RT (i.e., low frequency words were more difficult) and in the episodic retrieval task with our most sensitive measure of accuracy: D Prime scores (i.e., low frequency words were easier). Contrary to our hypothesis about the WFE, RT on the episodic retrieval task was the only factor that did not differentially affect the low

frequency words advantage prediction. Participants responded faster to the hits in the Difficult condition (high frequency) than in the Easy condition (low frequency) and no differences were observed between the two conditions RT's false alarms. Most of the literature concerning the WFE involves the recognition of single words (Reder et al., 2000; Balota, Burgess, Cortese, & Adams, 2002; Criss & Shiffrin, 2004a; Coane et al., 2011) and when using word pairs, most studies use an associative-recognition paradigm, where the word pairs are usually rearranged between study and test (Criss & Shiffrin, 2004b; Hockley & Niewiadomski, 2007; Badham et al. 2016) using one low frequency word and one high frequency word. One speculation to explain our inconsistent RT results during our episodic recognition task is that our study used the same word pairs during the retrieval test as they were presented during study (i.e., lexical-semantic judgment).

Finally, the observed interaction between age group differences by experimental task type provides independent evidence that the present difficulty manipulation successfully affected young and older adults differentially. One task adversely affected the younger adults, while the other task affected the older adults. Importantly, the two tasks were identical in every respect except for the type of memory judgment the participants completed. Our study is unique compared to other studies investigating the compensatory response because the majority of these studies employed tasks that were inherently more demanding for older adults, such as working memory (Capppell et al., 2010) or source memory (Cabeza et al, 2002) tasks. In addition, our difficulty manipulation relied on an *a priori* defined, objective criterion (i.e., word frequency) to vary difficulty at two separate levels in each task. This allowed us to investigate the

changes in brain activation as task demands increased in both tasks without needing to rely on performance in the task itself to define difficulty post hoc in order to compare high and low functioning groups of participants.

fMRI findings: Task-related activity across difficulty levels.

Both younger and older adults, regardless of level of task difficulty, showed strikingly similar brain regions activated in both tasks. First, in the lexical-semantic task, across all participants, our results support findings from previous studies investigating lexical-semantic processes (Cappa, 2008; Binder et al., 2009; Wang et al., 2010; Binder & Desai, 2011; Price et al., 2015) with brain activations in inferior frontal gyrus (IFG: orbital parts, operculum and triangular parts), dorsomedial PFC (DMPFC) including medial prefrontal cortex/supplementary motor area (SMA) and pre-SMA/superior frontal gyrus, left ventromedial prefrontal cortex (VMPFC), lateral and ventral temporal regions including fusiform gyrus and temporal cortex (superior, medial and inferior temporal gyrus), as well as bilateral parietal regions and posterior cingulate. Furthermore, our results are consistent with brain regions activated in tasks that required participants to make judgments comparing synonyms versus antonyms (Jeon et al., 2009), the semantic relatedness of words (Newman, Ikuta, & Burns Jr, 2010), implicit lexical-semantic processing (Kuperber et al., 2008) and other lexical, syntactic, and semantic judgments (Rissman et al., 2003; Ruff el al., 2008; Wright et al., 2011; Gan et al., 2013; for a meta-analysis see Rodd et al., 2015).

In the episodic retrieval, collapsing across levels of difficulty, we wanted to confirm that our task recruited the expected brain regions based on the literature. Both

age groups showed regions of activation associated with episodic memory retrieval including basal ganglia (thalamus, caudate and putamen), medial temporal lobe regions (i.e., hippocampus), posterior temporal-occipital gyrus, and fusiform gyrus, bilateral superior temporal gyrus, and bilateral superior, medial, middle and inferior prefrontal cortex, superior parietal lobule, precuneus and posterior cingulate (Wiggs et al., 1998; Hoscheidt et al., 2010; see Spaniol et al., 2009 for a meta- analysis and for a review see Dickerson & Eichenbaum, 2010).

Finally, for both tasks, the results indicated that older adults showed greater extent of activation in task-related regions, collapsing across levels of difficulty, compared to younger adults, consistent with previous literature (Grady et al., 1994; Cabeza et al., 2002; Park et al., 2010). On the surface, these "greater extents" in activation could be interpreted as a compensatory response among older adults, as originally proposed by Cabeza (2002), in which older adults are "working harder" due to underlying age-related structural and functional brain changes, thus resulting in greater brain activation compared to younger adults. However, the pattern of age-related increases in activation due to difficulty provide a very different picture (this pattern will be discussed in more detailed in the section: fMRI findings: Brain activity associated with increasing task difficulty).

fMRI findings: Brain activity associated with successful activity across tasks.

The current study used two novel tasks that share materials and general task requirements, our results of whole-brain activation during *task-general* or *shared* retrieval of lexical-semantic judgments and episodic memory not only replicate and

expands our *task-related* regions but also fit with the idea that such memory retrieval use an overlapping network engaging similar regions (Rajah & McIntosh, 2005; Burianova & Grady, 2007; Burianova, McIntosh, Grady, 2010; St-Laurent et al., 2011). It should be noted that both groups showed *task-general* activations occipital cortex, thalamus, medial-temporal, and prefrontal and parietal areas. This finding is particularly striking given that Spreng et al.'s (2010) meta-analysis suggests that when performance is unequal between older and younger adults, various regions across domains, which the authors refer to as Task Positive Regions (TPN), show age-related differences. Older adults engage thalamus, right BA 10 and 46, and Superior frontal gyrus (including pre- and post-central sulcus) to a greater extent compared to younger adults who most consistently engage ventral occipital regions (Spreng et al., 2010). Our *task-general* results showed that both age groups showed activation in the all regions described by Spreng et al. (2010) despite our age-related/task-depended behavioral differences previously described.

On the other hand, using a very liberal threshold, age-related differences in *task-specific* activity revealed that older adults showed extensive activations, mirroring the *task-related* results for the lexical-semantic task, for the *specific* task contrast they inherently find easier (lexical-semantic task > episodic retrieval task). While, younger adults engaged only right IFG, for the *specific* task contrast they inherently find easier (episodic retrieval task > lexical-semantic task). For the opposite contrast, the most difficult contrast (lexical-semantic task > episodic retrieval task) for younger adults, they showed activations in posterior regions, supporting Spreng et al.'s (2010) meta-analysis results. However, the observation that younger adults either engage posterior regions or

right IFG differs from Prince et al, (2007) results investigating overlapping and specific contribution of semantic and episodic memory with left hippocampus activations associated with episodic retrieval, bilateral temporal cortices and left IFG for semantic retrieval, and left IFG (middle and anterior ROIs) for overlapping retrieval processes. It should be noted that when we contrasted our experimental tasks against each other, we lowered our power to detect more robust activations, compared to the robust activations we observed for our *task*-related, task-*general*, and linear increases due to difficulty results. In fact, to investigate functional differences across experimental tasks such as semantic and episodic memory researchers have been comparing using overlapping activity to default network activity (Shapira-Lichter et al., 2013; Kim, 2016) or using multivariate methods as done by for example Grady and colleges (Rajah & McIntosh, 2005; Burianova & Grady, 2007; Grady et al., 2010), especially because of the well-known age differences in the cognitive processes behind the age-related performance of our experimental tasks (Grady et al., 2006; St-Laurent et al., 2011) although these results are not always consistent across studies (Oedekoven et al., 2013).

In addition to the *task-specific* age-related differences we observed, we hypothesized that younger adults were engaging regions differently than the older adults while performing each task. For example, in a previous study investigating age-related activation in episodic and semantic memory judgments, Berlingeri et al. (2010) used a similar design to ours by comparing younger and older adults on two semantic tasks (i.e., picture naming and sentence judgment) and two episodic memory retrieval tasks (i.e., picture recognition and sentence recognition). Their task-related activations are congruent with our results across all participants, although the authors only included one level of

difficulty in either domain (i.e., semantic or episodic) and they never compared the experimental tasks across each other. When they compared task-relevant left and right hemisphere hyperactivations (i.e., older > younger) and hypoactivations (i.e., younger > older), they showed differences in left IFG and inferior parietal lobule in the episodic tasks, but no differences were observed in the semantic tasks. It is important to note that we did not conduct between-group analyses at the task level as Berlingeri et al. (2010) did. Instead, we focused on between-group differences in linear activation increases in response to increasing difficulty.

Before discussing the difficulty effects fMRI findings, one caveat should be noted. In terms of our methodological approach, in the present study we investigated difficulty load by identifying the linear increases from the easy condition to the difficult condition using a parametric modulation. Prior research investigating brain activity in response to increases in task demand in other domains have led to several important considerations about how to best analyze fMRI data incorporating multiple levels of difficulty. The first initial method is just to investigate the activity associated with each condition greater than the control in each group. For example, Mattay et al. (2006) using the n-back contrasted 1-back greater than baseline, 2-back greater than baseline, and 3-back greater than baseline (see also Nagel et al., 2011). More recently Angel et al. (2016) reported old/new memory judgments (hits > correct rejections) for two difficulty levels in three groups: younger adults, and two older groups older: low and high performing.

A second method that researchers have used to investigate difficulty is by directly contrasting the hardest condition to the easy condition. For example, in their study of

relational encoding demands, Leshikar et al. (2010) compared related and unrelated pairs of pictures, assuming that relational encoding demands were greater for unrelated pairs of pictures. In their fMRI study, they assessed between age group effects by collapsing all pictures greater than baseline, and comparing this measure to related pictures greater than baseline and unrelated pictures greater than baseline. Leshikar et al. (2010) showed that in both older and younger adults there was increased activation in left IFG and left hippocampal regions as difficulty increased while participants judged/encoded pairs of pictures. Other cognitive domains that have used the same subtraction method investigate semantic processing (Wagner et al., 2001), visual searching (Ansado et al., 2013), and spatial judgments (Park et al., 2010; see also Rieck et la., 2017 and Kennedy et al., 2017). In the working memory domain, studies utilizing the n-back generally contrast high levels to lower of n-back load. For example, Nyberg et al. (2009) conducted a conjunction analysis that compared 3-back greater than 1-back and 1-back greater than baseline/rest. Finally, Cappell et al., (2010) contrasted 4-back greater than baseline, to 5-back greater than baseline, and 7-back greater than baseline.

A third method commonly used is to employ a parametric modulation analysis across the levels of difficulty. For example, Schneider-Garces et al. (2009) compared working memory load by including a regression parameter contrasting the linear increases from 2-back to 3-back to 4-back, and another linear increase from 4-back to 5-back to 6-back. Linear parametric modulation analyses have an advantage in understanding task demands as they reduce differences from sources other than difficulty (i.e., response selection, motor planning, and motor production) while distinguishing between difficulty-related increases and general task-related activity. This fMRI

parametric approach has been used successfully in other cognitive domains (e.g., Braver et al., 1997; Jonides et al., 1997; Schumacher et al., 2003, Daselaar et al., 2006, Nagel et al., 2008).

fMRI findings: Brain activity and effects associated with increasing task difficulty.

Although the common *task-related* networks were engaged strongly by both age groups, there were significant differences in the patterns of activation as difficulty increased by the two age groups. Specifically, our results showed that as task difficulty increased in the lexical-semantic task, younger adults showed increasing activation in task-related regions: left frontal regions associated with verbal processing (Binder et al., 2009), as well as additional contralateral regions. On the other hand, younger adults showed increases in bilateral posterior regions and right subcortical regions in the episodic retrieval task as difficulty increased. The younger adult's results suggest that in the task they find more difficult, they rely more in task-related regions and they even bring contralateral regions to deal with task demands, whereas in the task they find easier, they engage regions associated with visual processing.

Older adults showed a very different pattern as difficulty-related increases in activation in both tasks: in the lexical-semantic task, as difficulty increased, older adults showed increases in small but significant left hemisphere regions in PFC and occipital cortex. However, as difficulty increased in the episodic retrieval task, older adults showed increases in activation within the right hemisphere including frontal, temporal, parietal and posterior cortices, as well as medial regions (thalamus, precentral and medial frontal gyrus, cingulate gyrus). The older adult's results show that in the task that it is

hypothesized and behaviorally more difficult for older adults, we observe increases in activations in visual, sensory-motor, association (precuneus) and medial cortices. Also, the results are consistent the hemispheric encoding/retrieval asymmetry (HERA) model proposed by Tulving and colleagues (Tulving et al., 1994; Nyberg et al., 1996). We observed right involvement during episodic retrieval and left activations during semantic encoding with more widespread activations outside task-related regions in both tasks. There was no evidence that older adults showed more bilateral activations than the younger adults, and thus our linear increases due to difficulty results do not support the Hemispheric Asymmetry Reduction in OLDer Adults (HAROLD) model of cognitive aging (Cabeza, 2002)

A final noteworthy aspect of the activation pattern due to the difficulty main effect are the common regions for both groups in each task. As difficulty increased in the episodic retrieval task, both groups activated the thalamus and lingual gyrus. In the lexical-semantic task, as difficulty increased, both groups showed increases in a single task-related region: left IFG. Our finding here, is showing an age-invariant effect of the left-IFG as difficulty increased in a lexical-semantic task. This study is by no means the first to show the left IFG as a central region for semantic processing (Foundas et al., 1998; Rissman et al., 2003, Ruff et al., 2008) but also for controlled semantic retrieval, in particular, when task demands remain constant in younger adults (Wagner et al., 2001). Our results are consistent with recent results in aging research suggesting that language and other verbal abilities, such as lexical-semantic processing abilities, involve different patterns of activation in response to either age and increases in task demands (for a review see Shafto and Tyler, 2014). For example, Kennedy et al. (2014) used a cross-

sectional fMRI study to show that the left IFG remain unchanged by age increases when processing a semantic task that increases in difficulty. However, Davis at el (2014) reported two different language-processing networks, one that is affected due to task demands in a language task that resulted in increases domain-general regions (i.e., Opercular, Frontoparietal and bilateral PFC regions) and a second one that remains age-invarient but activated regardless of task demands in regions typically associated with language processing (i.e., parts of the *fronto-temporal network* –more specifically: left IFG (BA 45) and middle temporal gyrus.

fMRI findings: Age Group differences in the brain activity and effects associated with increasing task difficulty.

The primary focus of this study was to directly investigate age-related differences in patterns of fMRI activation as cognitive demands increased in two experimental tasks. Our results showed a double dissociation, mirroring our behavioral results. The between group comparisons (younger > older and older > younger) of linear increases confirmed that each age group showed greater increases in fMRI activity in the tasks where the behavioral accuracy decreased. Younger adults showed greater task-related regions compared to older adults in the lexical-semantic task as difficulty increased, while older adults showed greater increases in activation as task difficulty increased in the episodic retrieval task.

Direct age comparisons resulted in a large set of regions more active for older adults than younger adults in the episodic retrieval task. In contrasts, compared to older adults, in the lexical-semantic task younger adults activated left IFG, medial PFC and

midbrain, and bilateral posterior regions. No activations were observed for the opposite comparisons suggesting that for the task that we had hypothesized was easier for either of the groups, no significant age-related increases were observed. This finding is particularly striking given that age-related increases were observed only for the task the group inherently finds more difficulty. Thus, this suggest that using highly constrained tasks that only differed as a function of difficulty and that are expected to qualitatively interact with each group's inherent strengths and weaknesses resulted in a stronger dissociation. Our results indicate that increases in fMRI activation occur as an interaction between task difficulty and the inherent abilities of the individuals when facing a difficult task, rather than occurring only in older adults, or in older adults across all tasks, regardless of their a priori abilities in that domain. Furthermore, the present findings suggest that age differences were observed with older adults recruiting additional brain regions with increasing difficulty in the episodic memory task, which supports the HAROLD hypothesis (Cabeza. 2002).

Few studies to date exist to compare to the present results because of previously mentioned methodological differences at data processing, but also because few other studies have manipulated task demands using an *a priori* criterion. For example, taking a similar methodological approach, Schneider-Garces et al. (2009) investigated increases in verbal working memory (Sternberg memory search task) with several levels (low set sizes: 4-back > 3-back > 2-back and high set sizes: 6-back > 5-back > 4-back) in older adults and younger adults. Their results showed that as working memory load increased, older adults showed earlier limits to working memory capacity, at low set sizes paired with overrecruitment, and underrecruitments at high set sizes compared to younger

adults. Similarly, Toepper et al., (2014) used another working memory parading, Corsi Block-Tapping test (CBT) and showed also that activation increased with increasing age at low task demands and decreased with increasing age at high task demands. Both, Schneider-Garces et al. (2009) and Toepper et al., (2014)'s results can be interpreted as supporting the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) model (Reuter-Lorenz and Cappell, 2008). Our design and results cannot speak about the CRUNCH model, as we do not have sufficient levels of difficulty and because our difficulty load effects were parametrically investigated. Disentangling the age-related contribution of each level of difficulty in both tasks yielded insignificant results for the ROIs analyses we conducted. It is reasonable to speculate that in some of our ROIS, the increases between easy and difficulty were small, which made it difficult to track changes between the levels. Yet, our findings do at least provide an interaction between age and difficulty when it comes to the compensatory response. Our results differ from a recent study from Höller-Wallscheid et al., (2017) that showed that in three working memory tasks, compensatory response is a mechanism for the effects of individualized and/or subjective difficulty but not for age.

fMRI findings: Brain-Behavior relationships.

The most important prediction of the compensatory response is that additional recruitment is associated with better performance in older adults (Cabeza, 2002; Grady, 2012). To adequately investigate such association, we conducted correlation analyses between performance (accuracy or RT) and MR signal beta weights, but also we divided our groups based on their neuropsychological scores, a common strategy used to

investigate the compensatory response (Cabeza et al, 2002; Rosen et al., 2002; Duarte, Henson, & Graham, 2008; Angel et al., 2016; Meusel et al., 2017). Note that subdividing the groups have been done also according to the scores obtained during the performance of the task in the study (Nyberg et al., 2009; Sala-Llonch et al., 2012). In terms of our exploratory analyses, we decided to divide our groups using a priori measures, the younger adult group was divided based on their North American Adult Reading Test (NAART) and the older adult group based on an executive function score thought to represent executive function (Frontal) scores into high performers (see Glisky et al., 1995; Glisky et al., 2001).

We failed to find any consistent and strong evidence within the correlational analyses. In the lexical-semantic task, for both groups only activity in the superior frontal gyrus was negatively correlated with performance in the easy judgements. RT was positively correlated in the right cingulate and post-central gyrus for the younger adults in the easy condition. The older adults RT was correlated with activity in the right superior parietal lobule during the difficulty condition. In the episodic retrieval task, we found no significant brain and behavior correlations. Yet, other studies that are taken as evidence in support of a compensatory response have also failed to show a correlation between increases in activation and performance. For example, Cappell et al. (2010) reported a limited range of performance (accuracy and RT), making it difficult to obtain significant correlations between performance measures and the beta weights extracted in left and right ROIs (BA 9, 45 and 46) of their verbal memory task. It has been hypothesized that lack of brain-behavior correlations is due to truncated scores or ceiling effects. Correlations have been shown by Nagel et al. (2011) and Schneider-Garces et al. (2009)

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using a measure of "throughput" (a variable reflecting the amount information processed by each individual's memory span) as the performance variable. Other research has correlated difficulty related activity to errors (Toepper et al., 2014), a selectivity index (a measure of how strongly value affects memory; Cohen et al., 2016), an associative recognition accuracy index (or "pR"; de Chastelaine et al, 2016). It is important to note also that majority of studies showing the brain-behavior generally only investigate for correlations in one or two regions, for example, Lighthall, Huettel, and Cabeza (2014) studied only the ventromedial prefrontal cortex (vmPFC). We found correlations in one or two regions, yet we had no a priori hypotheses to those regions to task performance, making it difficult to draw any conclusions.

We further explored the brain-behavior relationship and found that in both tasks, our groups of high performers were the ones driving our difficulty increases results. The pairwise comparisons between either younger- high and low performing and older- high and low performing revealed the low-performing groups had no significant regions active as the tasks became more difficult. Furthermore, in the episodic retrieval task, the high-performing group of older adults showed activations in right IFG and middle gyrus that extends to sensory cortices compared to younger adults. In the lexical-semantic task it was the high-performing group of younger adults that showed the previously discussed regions active during task-related and linear increases due to difficulty results compared to older adults. Again, we did not find differences in levels of activation for the opposite pairwise comparisons. It is important to note that our exploratory analyses were aimed to understand variability between our groups yet by subdivided our groups we lowered our power, hence our low significant level. Nonetheless, our findings are striking at

understanding the compensatory response. For example, one region, the left IFG in the lexical-semantic task was engaged by both groups in the task-related results but also in the results showing the effects of difficulty. The left IFG was one of the verbal regions that also showed our age-related effects when we compared younger adults greater than older adults. As with Stebbins et al. (2002), the left IFG differentiated the younger to older adults. Furthermore, left IFG activation was only active when we compared high-performing younger adults to low-performing younger adults and to the older adults. These findings suggest that our brain-behavior relationship is modified not only by our age- and difficulty-related interaction but also by individual differences.

The compensatory response as a functional reorganization.

Our aim was to gain insight into age-related differences in the compensatory response when cognitive demands increased differentially for young and older adults. Cabeza and Dennis (2012) have delineated criteria that they suggest should be met in order to consider additional fMRI recruitment as a compensatory response: 1) the compensatory response has an inverted-U relationship with brain decline; 2) the compensatory response has an inverted U-shaped with task demands (note that this criterion is similar to the assumption included in the CRUNCH model (Reuter-Lorenz & Cappell, 2008); 3) the compensatory response is positively correlated with cognitive performance across individuals; and 4) the compensatory response is found in regions whose alterations affect cognitive performance in older adults. The current data are insufficient to tease apart some of the criterions since we do not have objective measures of brain decline or about alterations in regions that affect cognitive performance in older

adults. Also, because our study included only two levels of difficulty, it is impossible for us to consider the "inverted-U" function or the CRUNCH model.

The present study can only inform Criterion #3 (the compensatory response is positively correlated with cognitive performance across individuals). First, our results suggest that increases in fMRI activation as difficulty increases occur in the task that either group had more difficulty performing, although when difficulty was not accounted the two groups showed similar brain activations. Yet, correlational analyses did not show strong or consistent relationships between performance and the BOLD signal estimates in either task, for either age group. Yet, the exploratory analyses, after subdividing our age groups according on prior test performance (the NAART and a measure of executive functioning) taking into consideration for the groups a high degree of heterogeneity within the groups, suggest that the high-performing groups were the only ones showing successful compensation in the task behaviorally more difficult.

The present study provides novel information about the compensatory response by showing that neither age or task demands alone can account for the increases in brain activations usually assumed to be the compensatory response. The present findings show that each group showed different task difficulty effects, yet when we compared the two age groups as difficulty increased that is when our imaging results mirrored our behavioral results. Previous studies tend to ignore that the tasks are more difficult for the older adults (Cabeza et al., 2002) or they equate difficulty between age groups (Rajah et al., 2010; Manan et al., 2015; Höller-Wallscheid et al., 2017). The present findings support the view that increases in activation among older adults are likely a reflection of a more complex functional reorganization that is not restricted to increases in pure task

demands or age (Morcom, & Johnson, 2015). This likely occurs because of multiple

factors including age-related declines in cognitive processes such as executive functions

that result from age-related changes in brain structure and function.

Additionally, a possible explanation for our results is that both groups are

showing a functional reorganization, or "neural scaffolding" as described by The

Scaffolding Theory of Aging and Cognition (STAC) Park & Reuter-Lorenz (2009). By

this view, the compensatory response can be seen when a task becomes more difficult as

an adaptive brain response to any type of challenge. In older adults the challenge could be

a combination of extrinsic sources (i.e., task-demands) and intrinsic (i.e., age-related

changes in brain structure and function). In younger adults, the challenge would likely

come solely from extrinsic sources (i.e., task-demands), but this may also depend on a

different source of intrinsic demand arising from differences in experience and

knowledge. Supporting this notion, the activation data from our younger high performing

adults in the lexical semantic task suggests that the brain responds to increasing task

difficulty by using previously "arranged" brain circuitry (scaffolds) based on greater

vocabulary knowledge/experience, in comparison to low performers who have less of this

type of "scaffolding".

Limitations.

Despite providing new insights into the compensatory response as difficulty

increases, this study did have some limitations. The group sizes were relatively small,

which likely limited our power to detect differences when we subdivided our groups.

Future studies with larger sample sizes are needed to confirm our results, it is possible

this could impact the overall conclusions. Furthermore, our number of items in our design may have been limited within the two levels of difficulty when accounting for the incorrect responses we expected in the most difficult levels. We noted earlier such limitations, when we contrasted our experimental tasks against each other (*task-specific*) or the complementary exploratory analyses, we lowered our power to detect more robust activations, compared to the robust activations we observed for our *task*-related, task-*general*, and linear increases due to difficulty results. We did not analyze brain activity by comparing the two levels of both tasks (Difficult > Easy) or by comparing each level greater than the controls (ANOVA). However, we doubt that this would change our current results. One limitation of this study was the relatively small samples of young and older adults. Despite this limitation, significant differences between young and older adults were observed in both brain activation and difficulty. In addition, with respect to our older adults sample, is possible that we could have included only high performing older adults compared to the general population, as indicated by the group's high educational achievement, and may not be representative of the general population of older adults. Or in the other hand, it is possible differences among older adults reflects very early effects of incipient dementia or other underlying disease or genetic risk factor that we failed to screen and exclude.

Conclusions.

Together, the current study suggests the importance of the age-related brain's responsivity to task demands. We created two tasks with identical structure yet performance and difficulty differed. Although both age groups activated similar regions

while performing the two experimental tasks (*task-related* and *task-general*) there were differences regarding the way each group deals with increases in difficulty, especially for the tasks that were hypothesized more difficult depending in their a priori abilities. We observed also a significant interaction of age-related and task demand activity. Our results suggest that increases in fMRI activation as difficulty increases occur as an interaction to deal with task difficulty, the inherent abilities of the individuals and age. Future research will be needed to better understand the effect of each of those factors in the compensatory response of the brain.

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