Age-related changes in fMRI activity and cortical thickness in the prefrontal cortex during episodic memory in young vs. middle-aged adults

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Preface & Contribution of Authors

Dr. Natasha Rajah, David Maillet, and Stamatoula Pasvanis collaborated on the fMRI portion of this study which has been submitted to a publication for review. Stamatoula Pasvanis aided in participant recruitment and data collection, David Maillet helped conduct the fMRI analysis, and Dr. Natasha Rajah assisted in analyzing the results. The primary author of this thesis, Diana Kwon, contributed to all parts of the process. The cortical thickness analysis was completed independently.

Abstract

Healthy aging is associated with episodic memory decline and spatial and temporal context memory tasks are particularly sensitive to decline with age. Studies have shown that older adults perform significantly worse than young adults on context memory tasks by age 60, and have related this to changes in prefrontal cortex (PFC) structure and function. More recently, studies have revealed that context memory declines are apparent at midlife, yet we know little about the changes in brain areas associated with context memory at this stage in life. To investigate context memory and its neural correlates at midlife we conducted an in vivo event-related fMRI study in which healthy middle aged adults (40-55 yrs old; n=27) and young adults (18-35 yrs old; n=22) performed spatial and temporal memory tasks for faces. Two versions each task (easy and difficult) were administered to allow for differentiation between age-related and performance-related effects. Subjects were scanned during both encoding and retrieval. Behaviorally, middle-aged adults performed significantly worse on spatial hard, temporal easy, and temporal hard tasks compared to young adults. There were both similarities and differences in the patterns of brain activity observed in young and middle aged adults during successful context memory encoding and retrieval. Young and middle-aged adults exhibited similar activity in the left MPFC and left VLPFC at encoding and bilateral DLPFC at retrieval. MPFC activity negatively predicted hard task accuracy in young adults and positively predicted easy task accuracy in middle-aged adults in both task types. Young adults recruited the left APFC to a greater extent during retrieval vs. encoding but middle-aged adults did not. Moreover, activity in this region was positively predictive of accuracy on hard tasks in young adults. Middle-aged adults exhibited greater activity in a variety of right PFC regions during hard vs. easy retrieval tasks, compared to young adults. In addition to functional changes in the brain, I also observed age-

related cortical thinning in the bilateral DLPFC and the left VLPFC. These results together indicate that context memory decline is apparent at midlife and is associated to functional and structural changes in the PFC.

Résumé

La vieillesse est associée à un déclin de la mémoire épisodique et spatiale et les tâches situes dans un contexte temporel sont particulièrement sensibles au déclin avec l'âge. Des études ont montrées que des quarantenaires réussissent nettement moins que de jeunes adultes sur des tâches utilisant la mémoire contextuelle des l'âge de 60 ans et ont reliées ces résultats aux changement dans la fonction et la structure du cortex pré-frontal (PFC). Récemment, des études ont révèle que le déclin de la mémoire contextuelle apparaît des la quarantaine, mais nous ne connaissons que très peu les changements dans les zones du cerveau associées a la mémoire contextuelle à cet âge la. Pour étudier la mémoire contextuelle et ses corrélations neurales pendant la quarantaine, nous avons conduit une étude fMRI in-vivo en situation dans laquelle des adultes en bonne santé (de 40 a 55 ans, n=27) et de jeunes adultes (de 18 a 35 ans, n=22) ont effectues des tâches utilisant la mémoire spatiale et temporelle pour des visages. Deux versions de chaque tâche (facile et difficile) ont été effectuées pour faire la différence entre les effets lies à l'âge et les effets de performance. Les sujets ont été surveilles durant l'encodage et la récupération. D'un point de vue comportemental, les quarantenaires significativement moins bien exécute les tâches spatiales difficiles, temporelles faciles et temporelles difficiles compares aux jeunes adultes. Il y a eu des similitudes et des différences en terme d'activité cérébrale observées chez les jeunes adultes et les quarantenaires pendant les encodages et récupérations de la mémoire contextuelle. Les jeunes adultes et les quarantenaires ont montre des activités

similaires dans les MPFC et VLPFC gauche a l'encodage et le DLPFC bilatéral a la récupération. L'activité du MPFC a prédit négativement la précision des tâches difficiles chez les jeunes adultes positivement la précision des tâches faciles chez les quarantenaires. Les jeunes adultes ont davatange utilise l'APFC gauche pendant la recuperation que lors de l'encodage contrairement aux quarantenaires. De plus, l'activité dans cette region a predit positivement la precision des tâches difficiles chez les jeunes adultes. Les quarantenaires ont montre une plus d'activités dans une variete des regions du PFC droit pendant les tâches difficiles de recuperation contraitement aux jeunes adultes. En plus des changements fonctionnels du cerveau, j'ai aussi observe un amincissement corticale dans le DLPFC bitateral et le VLPFC gauche. Ensemble, ces resultats indiquent une regression de la memoire contextuelle a la quarantaine et qu'elle est associee au changements fonctionnels et structurels dans le PFC.

Table of Contents

List of Abbreviations

BA - Brodmann area

EM – episodic memory

MTL – medial temporal lobes

PFC – prefrontal cortex

DLPFC – dorsolateral prefrontal cortex

VLPFC – ventrolateral prefrontal cortex

MPFC – medial prefrontal cortex

AFPC – anterior prefrontal cortex

fMRI – functional magnetic resonance imaging

ERP – event-related potential

PLS – partial least squares

CRUNCH – compensation-related utilization of neural circuits hypothesis

GMv – gray matter volume

eSE – Encoding Spatial Easy

eSH – Encoding Spatial Hard

eTE – Encoding Temporal Easy

eTH – Encoding Temporal Hard

rSE – Retrieval Spatial Easy

rSH – Retrieval Spatial Hard

rTE – Retrieval Temporal Easy

rTH – Retrieval Temporal Hard

List of Tables

List of Figures

1. Introduction

Overview

Remembering the place you left the keys, the venue for your last birthday party, and the location of your first kiss are all examples of episodic memory. Episodic memory is a subset of declarative (explicit) memory encompassing the ability to encode, store, and retrieve information about past personal events (Tulving, 1984). Loss in episodic memory occurs during the normal aging process, and can lead to a decrease in quality of life (Mol et al, 2007; Borson, 2010).

Not all forms of memory are afflicted with age; studies of episodic memory and aging have found that performance on recognition memory tasks stays relatively intact while memory for the spatial (where) and temporal (when) context of past events (context memory) declines (Maillet & Rajah, 2011; Spencer & Raz, 1995; Wegesin et al, 2002; Naveh-Benjamin, 2000). Recent evidence suggests that this decline in context memory may begin as early as middle age (Cansino et al, 2010) along with associated changes in structure and function of the brain (Salat et al, 2004; Grady et al, 2006; Cansino et al. 2010, 2012; Park et al, 2013).

In order to understand the process of memory loss over the lifespan, it is important to assess the changes occurring at earlier stages of life. To address this, the following study assessed contextual memory at midlife by comparing the memory-related functional and structural changes in the brains of young (aged 18-35 years) and middle-aged (aged 40-55 years) adults. The focus of the study was the prefrontal cortex (PFC), as it has demonstrated the earliest signs of volumetric reductions (Fjell et al, 2009; Salat et al, 2004; Raz et al, 1997) and task-related under- and over-activation (Grady et al, 2006; Park and Reuter-Lorenz, 2009; Kennedy et al, 2012; Park et al, 2012) with age.

Aging and contextual memory decline

There are a number of possible reasons for the more rapid decline of contextual memory with age than recognition memory. Memorizing the contextual details of an event requires the binding of an item with the associated details (i.e. location, time). This associative process is thought to be mediated by the medial temporal lobes. In addition, context memory tasks place greater demands on executive processes at both encoding (e.g. assessing multiple features, shifting attention or cumulative rehearsal) and retrieval (e.g. decision making) (Parkin and Walter, 1992; Chalfonte and Johnson, 1996; Mitchell et al, 2000; Dulas and Duarte, 2011). These processes are thought to be dependent on the function of the PFC, an area of the brain that is particularly sensitive to decline with advancing age (Spencer and Raz, 1994). Consistent with the idea that the PFC is particularly important for mediating context vs. recognition memory; studies have shown that patients with frontal lobe lesions exhibit deficits in source and temporal memory, but show intact recognition memory (Shimamura & Squire 1991; McAndrews & Milner, 1991), pointing to the critical role of frontal processes in contextual memory maintenance. Therefore, the PFC is the primary region of interest to study the causes of contextual memory loss at middle age.

Prefrontal cortex function at midlife

The PFC is thought to be responsible for the executive control processes – such as updating information, monitoring, selection, response inhibition, and attention orientation – that contribute to episodic memory (Fletcher & Henson, 2001; Ranganath et al, 2003).

Recent studies have begun to shed light on the neural changes contributing to episodic memory decline at midlife (Grady et al, 2006; Cansino et al. 2010, 2012; Park et al, 2012). At middle age, performance on recognition memory tasks stays intact but changes in neurobiology

occur (Grady et al, 2006; Kennedy et al, 2012; Park et al, 2012). Grady et al (2006) conducted an fMRI study examining neural activity during encoding and retrieval in young, middle-aged, and older adults while they performed recognition memory tasks. They found linear decreases with age in task-related regions such as the dorsolateral prefrontal cortex (DLPFC) and linear increases of activity in task-unrelated ("default network") regions (e.g. medial frontal and parietal regions) at both encoding and retrieval.

Studies assessing encoding activity during a subsequent memory paradigm have also found task-related over-activation with successful encoding in the lateral PFC with age (Cabeza et al, 2004; Cappell et al, 2010; Kennedy et al, 2012). Using a sample of healthy adults aged 30 – 89 years, Kennedy et al (2012) found a dose-dependent relationship between beta-amyloid load and the activation of task-dependent regions and suppression of default network regions. Increased amyloid load led to decreased activation and suppression across the lifespan (even in young and middle-aged adults). The areas of the PFC that showed reduced activation with amyloid load were found in previous studies (Cabeza, 2002; Cabeza 2004; Cappell et al, 2010) to be over-recruited by older adults. Beta-amyloid is a hallmark characteristic of Alzheimer's disease and the reduced activation of task-related areas and suppression of task-unrelated areas with increasing beta-amyloid load suggest that it may contribute to memory loss by interfering with the potential compensatory recruitment (Cabeza, 2002) of the DLPFC.

In a study comparing neural activity in the three age groups (young, middle, and old) during a recognition memory task, Park et al (2013) identified age-common activations in the medial temporal and bilateral ventrolateral prefrontal areas during encoding, and they found reduced activation at middle age in bilateral occipital, temporal, and parietal cortices; task-related regions linked to positive subsequent memory effects in young adults. Taken together, the

neuroimaging studies with middle-aged adults reveal different patterns of change in the prefrontal cortex during recognition memory tasks, and further analysis is required to identify what causes the differences and what effect they may have on performance.

To date, the only studies assessing contextual memory at middle age have been conducted using event-related potentials (ERPs). In a series of studies, Cansino et al (2010, 2012) revealed that contextual memory decline at middle age is associated to changes in the frontal cortices during encoding and retrieval. During encoding, a late-onset positive waveform at the right lateral frontal cortex was progressively delayed across the middle and old age groups compared to the young group, suggesting a loss in efficiency of encoding mechanisms with age (Cansino et al, 2010). At retrieval, there was no significant difference in amplitude in retrieval success, though the right frontal effect during unsuccessful retrieval attempts became delayed, shorter, and relatively smaller with advancing age; additionally, this activity was only found to relate to performance only in young adults (Cansino et al, 2012)

Age-related structural changes in the PFC

Aging is associated with widespread thinning of the cerebral cortex (Fjell et al, 2009), and this global thinning is evident by middle age (Salat et al, 2004).

Raz et al (1997) conducted one of the preliminary studies assessing the structural integrity of the cerebral cortex with age. Using a manual segmentation protocol on structural images of 148 healthy adults aged 18-77, they found widespread linear-trends for gray matter volume (GMv) loss across the cortex, with the steepest age-related decline in the prefrontal cortex, namely the dorsolateral and orbital frontal cortices (areas involved in executive functioning processes such as decision-making and monitoring processes). This linear change in prefrontal cortex volume has been consistent across studies assessing age-related structural

changes (Kramer, 2007; Giorgio et al, 2010). In an analysis combining samples from 6 different studies for a total of 883 participants across the lifespan (18-93 years), Fjell et al (2009) conducted cortical thickness analysis by using reconstructed gray/white matter representations and automated thickness measurements. As seen previously, age was associated with thinning across most of the cortical surface. The largest age effects were found in the prefrontal cortex, specifically in the superior, middle, and inferior frontal gyri.

Additionally, studies have replicated these results and looked at whether these effects could be seen earlier in life. Salat et al (2004) conducted cortical thickness analysis on 106 healthy participants in the young (18-31), middle age (41-57), and old age (60-93) groups. Cortical thickness was assessed by measuring the distance between the grey/white matter boundary and the cortical surface from an averaged structural scan of 2-4 images for each participant. The researchers then computed a general linear model for the effects of age on thickness. They found a significant age effect on cortical thickness with a widespread decrease in cortical thickness in both the left and right hemispheres. Thinning was most predominant in the prefrontal cortex, but the temporal cortex and the parahippocampal cortex were relatively spared. In a subsequent analysis where they looked at the age effect in only the young and middle-aged adults groups, they identified that this decrease was apparent by middle adulthood.

These results provide evidence of age-related overall cortical thinning and volumetric reduction across the brain; with the greatest amount of decline in the PFC. There is also preliminary evidence that these changes are apparent as early as middle age. How this loss in structural integrity might relate to functional changes and contextual memory abilities is discussed below.

Associations of structure and function with aging

Recently, researchers have been assessing the relationship between structural and functional changes with age. Meta-analysis of studies reveals converging evidence that patterns of activity are dependent on older adults' performance (Spreng, 2010; Mallet & Rajah, 2013).

As discussed earlier, aging is associated with gray matter loss in the frontal cortices. Researchers have found both negative and position associations of PFC volume and function with age (Brassen et al, 2009; Kalpouzos et al, 2012). Kalpouzos et al (2012) gathered both structural and functional data in young and older adults while they performed a recognition memory task and conducted voxel-by-voxel correlations and ANOVAs with gray matter volume (GMv) as a covariate. They found that older adults' performance on the task matched that of young adults, and that there was a negative correlation between DLPFC volume and the corresponding activity in that region in older adults; GMv volume showed a decrease and functional activation showed an increase. Alternatively, a similar study was conducted by Brassen et al (2009) which assessed brain structure and function in young and older women during recognition memory tasks. In this study, older adults performed more poorly on the tasks, and there was a positive correlation between GMv and functional activity. In this case, they found a similar decrease in PFC GMv, but there were task-related decreases in DLPFC. These studies provide evidence for the compensation-related utilization of neural circuits hypothesis (CRUNCH) model (Reuter-Lorenz & Cappell, 2008), which suggests that older adults will recruit additional brain areas to account for increasing task demands and age-related structural and functional deficits occurring in the brain.

Overall, two major patterns of change in the PFC are found in studies of cognitive aging: 1) decreased activity in the PFC with age and 2) increased activity in the PFC with age. The

reductions in activity may display a functional deficit while increased activity may be the result of neural inefficiencies, compensatory activation, or dedifferentiation. The neural inefficiency hypothesis describes overactivation as a result of reduced processing efficiency in the PFC, possibly due to underlying pathology in grey matter volume, neurochemistry, or white matter connectivity (Morcom et al, 2007). The increase in activity is interpreted by some as compensation for the neural inefficiencies (increased "noise" in processing) caused by age or decline of function in other areas of the brain (Cabeza, 2002; Reuter-Lorenz & Cappell, 2008). Finally, the dedifferentiation hypothesis describes the age-related differences in functional activation as deficits in neurotransmission that leads to less distinct neural representations; the increased activation reflected reduced specialization of function that may or may not be compensatory (Li et al, 2001).

Goals and Hypotheses

To date, there are no studies assessing how changes in cortical thickness and fMRI activity in the PFC relate to the context memory changes observed at midlife. This study was conducted to bridge the gap in understanding of what happens during the lifespan by identifying changes that occur at middle age. The current study examined behavioural performance, functional activity, and cortical thickness in middle age vs. young adults. To do so, participants performed spatial and temporal contextual memory tasks while neural activity was acquired in an MRI scanner. Non-rotated partial least squared (PLS) analysis was conducted to identify functional differences between tasks, across task conditions. Structural scans of each participant were gathered for cortical thickness analysis to measure changes in gray matter morphology. This experimental paradigm allowed the examination of 1) age-related functional and structural

changes specific to middle age and 2) the relationship between behaviour and structural and functional changes in the brain.

The hypotheses were that compared to young adults, middle-aged adults would perform more poorly on context memory tasks (Cansino et al, 2012) and that this difference would be greater in difficult (high memory load) tasks. Functionally, it was predicted that compared to young adults, middle-aged adults would exhibit functional changes in the task-related regions of the prefrontal cortex, specifically in the dorsolateral prefrontal cortex (Cansino et al, 2012; Grady, 2006). Additionally, it was expected that the left DLPFC and right APFC would demonstrate functional compensation because of these structural and functional changes (Rajah et al, 2010). Structurally, it was predicted that middle-aged adults would exhibit age-related thinning in the cortex compared to young adults, specifically in the prefrontal cortex (Salat et al, 2004; Raz et al, 1997). Finally, it was expected that there would be overlap in the areas where the functional and structural changes were found.

5. Experimental methods

5.1 Study participants

27 young (age range 20-35 yrs, mean age 26.85, mean education 16.44 yrs, 18 females) and 22 middle-aged adults (age range 40-55 yrs, mean age 46.86, mean education 15.77 yrs, 15 females) participated in this study. Subjects were recruited from the Montreal community using local advertisements and referrals. The advertisements called for young adults between the age of 18-35 and middle-aged adults between the age of 40-55 who had completed high school, were right-handed, and fluent in English or French. Our lab has several years of experience creating advertisements, screening and recruiting healthy participants for studies that have been conducted in the past years (Rajah & McIntosh, 2005; Rajah et al, 2010).

Subjects were screened for history of neurological and psychological illness. All subjects were right-handed as measured by The Edinburgh Inventory for Handedness (Oldfield, 1971). We administered the following battery of neuropsychological tests to screen out individuals suffering from psychiatric symptoms and dementia and to obtain measures of memory and language function: the Mini-International Neuropsychiatric Interview (M.I.N.I.) [inclusion cut-off score ≤ 2, (Dahmani, 2012), Montreal Cognitive Assessment (MOCA) [exclusion cut-off score < 27, (Folstein, Folstein, & McHugh, 1975)] the Beck Depression Inventory (BDI) [inclusion cut-of < 15 (Beck, 1987)], the California Verbal Learning Task (CVLT) [exclusion cut off determined per case using age & education (Norman, Evans, Miller, & Heaton, 2000) the American National Adult Reading Test (NART) [inclusion cut-off ≤ 2.5 SD (Spreen & Strauss, 1997). Only those subjects who met all the cut-off criteria were invited to participate in the scanning session. Additional medical exclusion criteria included having a history of or current diagnosis of diabetes, cataracts, and glaucoma; and a current diagnosis of high cholesterol levels and/or high blood pressure left untreated in past 2 years. Moreover, anyone having a first-degree relative with Alzheimer's disease was excluded from the study.

One-way between group analyses of variance (ANOVAs) were conducted on mean years of education and all neuropsychological measures to determine the existence of significant group differences (significance threshold $p < .05$) using SPSS for Windows (Version 17.0). All participants signed a consent form approved by ethics boards of The Douglas Hospital, the Montreal Neurological Institute (MNI), and McGill University.

5.2 Stimuli

The stimuli used for the task were black-and-white photographs of age variant human faces that were cropped from the neck upwards and rated as either neutral or pleasant by two

independent raters. The stimuli were used in prior fMRI studies of memory function conducted by our lab (M. N. Rajah, Ames, & D'Esposito, 2008; M. N. Rajah, R. Languay, & L. Valiquette, 2010) and details about the stimuli can be found in Rajah et al. (2008; 2010). The stimuli used for each memory task were balanced for age, sex, and neutral/pleasantness rating.

5.4 Task paradigm

Subjects were told that they were participating in a computer-based visual nonverbal memory experiment. They completed 12 fMRI scanning runs while performing easy and hard versions of spatial and temporal context memory tasks. Both spatial and temporal tasks were used to allow for differentiation of task-general and task-specific neural correlates of spatial and temporal context memory in both age groups. The easy-hard manipulation allowed the discrimination of functional changes associated with age main effects, performance main effects, and age and performance interactions. E-Prime (Psychology Software Tools Inc.; Pittsburgh, PA, USA) was used to present the behavioural protocol and collect accuracy and reaction time (RT; msec).

Each run consisted of 3 experimental blocks: 1 hard spatial *or* 1 hard temporal context memory task, 1 easy spatial context memory task and 1 easy temporal context memory task. Each run was approximately 9 minutes long. Each subject performed a total of 24 blocks: 6 hard spatial, 6 hard temporal tasks, 12 easy spatial and 12 easy temporal tasks. The task order was counter-balanced within run and run order was counter-balanced across subjects. An instruction screen was presented prior to each task to inform the subject of which task was to follow.

Encoding blocks

Prior to encoding, a 10-second instruction screen appeared to inform the subjects to memorize either the spatial location or temporal order (depending on the task) of face stimuli

(see Figure 1). Face stimuli appeared one-by-one to either the left or right of a fixation cross on the screen. Subjects viewed 6 unique encoding stimuli in the easy task and 12 encoding stimuli in the hard tasks. This difference in load (6 or 12 stimuli) constituted the difficulty manipulation. Each encoding stimulus was presented for 2 seconds, with a variable intertrial interval (ITI) (2-8 sec, mean ITI = 5.13 sec). Subjects rated each face as "pleasant" or "neutral". The neutral/pleasantness rating was incorporated so that the social-emotional evaluations could aid in memorizing the faces (Grady et al., 2002).

After each encoding block, subjects performed a 1-minute long alphabetizing distractor task to prevent working memory rehearsal and ensure the stimuli were stored in long-term memory. For this task, subjects indicated which word comes first alphabetically in five word pairs (5 sec/word pair). ITIs were varied between each pair.

Retrieval blocks

Subjects were presented with 3 retrieval events during the easy tasks and 6 retrieval events in the difficult tasks. Each retrieval event consisted of two of the face stimuli from the preceding encoding list. For temporal context retrieval, participants were asked indicate which face was seen MOST recently or LEAST recently. With spatial context, participants were told to indicate which face appeared on either the LEFT or RIGHT side of the screen. During retrieval, stimuli were presented vertically (to the top and bottom of a fixation cross) to prevent perceptual bias effects since the encoding stimuli were presented horizontally (see Figure 1). The temporal distance between the retrieval items were randomized. Each retrieval stimuli appeared for 6 seconds, with a variable ITI. All motor responses were made with the subject's right (dominant) hand.

5.5 fMRI data acquisition

Subjects were scanned in a 3T Siemens Trio scanner at the Douglas Brain Imaging Center. They were asked to lie in a supine position in the MRI scanner while wearing a standard head coil. AT1-weighted structural volumes were acquired at the start of the experiment using a 5 min gradient echo (GRE) ADNI (Alzheimer's Disease Neurimaging Initiative) sequence (TR = 2300 msec, TE = 2.98 msec, flip angle 9º, 176 1mm sagittal slices, 1x1x1 mm voxels, FOV 256mm^2). BOLD (functional) images were acquired using a single-shot T2-weighted gradient EPI pulse sequence (TR = 2000 msec, TE = 30 msec, FOV = 256mm^2, matrix size = 64x64, in-plane resolution = 4x4 mm) while subjects conducted the aforementioned behavioral tasks. Each whole brain was imaged along the anterior-posterior commissural plane and contained thirty-two oblique slices of 4.0 mm thickness with no gap. A mixed rapid event-related experimental design was used. Jitter was added to image acquisition trials by making the inter-trial intervals variables. (range: 2-8s; mean ITI of 4.66 s). Visual stimuli were generated by a PC computer and back-projected onto a screen placed at the scanner bore, which were made visible to participants by a mirror mounted within the standard head coil. E-Prime presentation software (Psychology Software Tools Inc.; Pittsburgh, PA, USA) was used to run the experimental protocol and collect behavioral data. Participants requiring correction for visual acuity wore plastic optical corrective glasses. Subjects responded on a fibre optic 4-button response box during experimental tasks.

5.6 Behavioral data analysis

To examine main effects and group-by-task interactions, a between group repeated measures task (2: temporal, spatial) x difficulty (2: easy, hard) ANOVA (sig. threshold $p<0.05$) was conducted using SPSS for Windows (ver. 17.0). Accuracy and reaction time were compared between young and middle-aged adults. Post hoc analyses were conducted to clarify results.

5.7 fMRI processing and analysis

Images were reconstructed from raw k-space and converted to ANALYZE format. Subsequent image processing was conducted with SPM8 software (http://www.fil.ion.ucl.ac.uk/spm) run with MATLAB 7.13 (www.mathworks.com) on a Linux platform. Images from the first 10 sec of each were discarded to control for field in-homogeneities. Functional images were spatially realigned to the first image acquired to correct for movement artefact, using a 6 parameter rigid body spatial transform and a least squares approach. Subjects with head motion greater than 3mm were discarded from the analysis. Individual subjects' functional images were spatially normalized to the MNI EPI-template available in SPM8, to place them in a standard coordinate space based on the Talairach atlas (Talairach and Tournoux, 1988) to facilitate group analysis and report activations in standard Tailarach-space. Volumes were resampled into 4mm cubic voxels and smoothed using 8mm full-width half-maximum (FWHM) isotropic Gaussian kernel, to minimize inter-participant anatomic variability (Friston, 2004). Multivariate spatio-temporal partial lease squares (PLS) were conducted on fMRI data with PLSGUI software (http://www.rotman-baycrest.on.ca/index.php?section=84). For all analyses, only the data from *correct* encoding and retrieval events were analyzed. Any subject with less than 14 correct events were discarded from the analysis.

5.8 Cortical thickness processing and analysis

Before measuring cortical thickness, cortical reconstruction and volumetric segmentation were conducted on anatomical scans using previously processed algorithms in the FreeSurfer software package (http://surfer.nmr.mgh.harvard.edu/). Each scan underwent motion-correction (Reuter et al, 2010) and removal of non-brain tissue (Ségonne et al, 2004). Skulls were removed

with a skull-stripping algorithm (Ségonne et al., 2004). Then the scans went through segmentation of the subcortical white matter and deep grey matter, intensity normalisation (Dale and Sereno, 1993; Dale et al., 1999; Fischl et al., 1999a), and tessellation of the white/gray matter boundary, automatic topology correction and surface deformation to optimize the gray/white and gray/CSF borders (Fischl et al., 2001; Ségonne et al, 2007). Finally, the brains underwent surface inflation (Fischl et al., 1999a), registration to an atlas of cortical folding patterns across subjects (Fischl et al, 1999b), parcellation of the cerebral cortex based on previously determined cortical maps based on gyral and sulcal structures (Desikan et al., 2006; Fischl et al., 2004), and creation of maps of curvature and sulcal depth of the cortical surface. Signal intensity and continuity information from the structural scans were used to measure cortical thickness, which the program detects as the closest distance from the grey/white matter boundary to the grey/CSF boundary on the tessellated surface (Fischl and Dale, 2000). Signal intensity is measured across tissue classes rather than absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data and can detect submillimeter differences. The images were smoothed (20 mm full-width at half-maximum (FWHM) surface-based Gaussian kernel and group analysis was conducted with Qdec GUI in the FreeSurfer package. Qdec was used to conduct a general linear model (GLM) analysis of age and cortical thickness with age as a continuous variable.

Non-rotated PLS

Analysis of the fMRI was conducted using the "Non-Rotated PLS" option in the PLSGUI software (McIntosh et al, 2004) to assess task- and age-related similarities and differences in event-related brain activity. The following contrasts were assessed: (1) correct spatial-easy context encoding (2) correct temporal-easy context encoding (3) correct spatial-hard context

encoding (4) correct temporal-hard context encoding (5) correct spatial-easy context retrieval (6) correct temporal-easy context retrieval (7) correct spatial-hard context retrieval (8) correct temporal-hard context retrieval. Between-group data matrices were made with fMRI data for both groups – each row of the datamat represented event-related activity for each event type and the columns represented the signal from each voxel at each time lag, which contains data for a 2-second period. The first time lag coincided with event onset. There were 8 time lags for a total of 16s after event onset to account for the entire breath of the hemodynamic response function (HRF). The signal was zeroed at event onset and expressed at a percentage deviation from baseline in subsequent time lags.

5.9 Linear Regression Analysis – Predicting Accuracy from Brain Activity and Cortical Thickness

To examine whether age-related increase in activity was compensatory, the brain-behaviour associations in the PFC for young and middle-aged adults were assessed. This was done using SPSS to conduct within-group backward step-wise regressions to examine whether the significant PFC regions from the PLS analysis and cortical thickness analysis would relate to retrieval accuracy during the easy and hard tasks. The dependent variable was mean retrieval accuracy and the predictor variables included for functional activity were the mean baseline corrected activity during lags 2-4 for a 1 mm sphere surrounding the significant PFC peaks from the PLS results and for structure were the mean thickness values for the PFC regions of interests (ROIs).

Multicollinearity was assessed by assessing the tolerance value ($t < 0.2$) nor variance inflation factor ($VIF > 5$) (Mason, 1991; O'Brien, 2007) in the significant models. Correlations were also examined among the ROIS values (wthin group) to verify to verify that none of the

predictor variables exhibited a correlation equal to or greater than 0.80 with any of the other variables in the models (Mason, 1991). Competing models were eliminated using the R-change and F-statistic change ($p > 0.05$) from removing a predictor variable to see if it was acceptable to remove from the model. Only beta-values for significant reduced models that predict accuracy are reported.

6. Results

Neuropsychological results

See Table 1 for group means for education (in years) and scores for each of the administered neuropsychological tests. A significant group difference was found in the CLVT long-form free recall test [$F(1,48)=4.641$, $p=0.036$]. No other significant group differences were found.

Behavioural results

See Table 2 for the mean and standard error of group accuracy and reaction time (ms) on all four tasks (spatial easy, spatial hard, temporal easy, temporal hard).

The task (2: temporal, spatial) x difficulty (2: easy, hard) x group (2: young, middle) repeated measures ANOVA for retrieval accuracy revealed significant task [$F(1,47)=267.87$ $p<0.001$], difficulty [$F(1,47)=29.53$ $p<0.001$] and group [$F(1,46)=10.64$, $p=0.002$] main effects and significant task*difficulty [$F(1,47)=5.29$ $p=0.03$] and task*group [$F(1,47)=8.57$ $p=0.005$] interaction effects.

Post hoc paired-sample T-tests for task and difficulty revealed that the task*difficulty interaction was driven by the significant difference between the easy and hard condition in the temporal task [$T(1,48)=2.186$ $p<0.001$] but not the spatial task [$T(1,48)=4.799$ $p<0.034$]. A post-hoc one-way ANOVA for task and group indicated that the significant group differences in

the temporal [T(1,47)=3.864, p<0.001] but not in the spatial [T(1,47)=1.85, p=0.07] tasks was driving the task*difficulty interaction. Further analysis revealed that the absence of a significant effect for spatial tasks was a result of the significant differences in performance on the spatial hard [T(1,47)=2.35, p=0.023] but not the spatial easy task [T(1,47)=0.795, p=0.43].

The task (2: temporal, spatial) x difficulty (2: easy, hard) x group (2: young, middle) repeated measures ANOVA for reaction time revealed significant main effects of task [F(1,47)=47.08, p<0.001] and difficulty [F(1,47)=19.96, p<0.001] main effects. There were no significant group main effects or interactions found.

Between group non-rotated PLS results

Four significant latent variables (LVs) were found: 1) LV 1: main effect of Encoding vs. Retrieval (p<0.001; 42% cross-block variance), 2) LV 5 : main effect of Easy vs. Hard Retrieval (p=0.004, 8% cross-block variance), 3) LV 6: interaction of Group-by-Encoding vs. Retrieval (p=0.014; 7% cross-block variance), and 4) LV 10: interaction of Group-by Easy vs. Hard Retrieval (p <0.001; 13% cross-block variance). The results for each LV are presented in Tables 4-7 and Figures 1-4. Only peak coordinates from time lags 2-4 (2-8 seconds post-stimulus onset) are presented because temporal brain scores indicated that task differences were maximal at these time lags. If peak coordinates were found in more than one time lag, only the coordinates where the bootstrap ratio was maximal are reported. Given the interest was primarily the prefrontal cortex, significant ROIs were extracted (marked with asterisks on Table 4-7) and activation profiles were plotted.

LV1: Encoding vs. Retrieval Main Effect

Figure 2A and Table 4 present the whole-brain PLS results for LV 1: neural activity during correct encoding vs. retrieval events in the young and middle-aged groups. This contrast identified regions differentially activated during all successful encoding events (eSE, eSH, eTE and eTH; Figure 2A, red represents positive saliences) vs. all correct retrieval events (rSE, rSH, rTE and rTH; Figure 2A, blue represents negative saliences). At encoding vs. correct retrieval, both age groups exhibited greater activation in the medial occipital cortex (BA 17), left ventrolateral PFC (VLPFC; BA 47), left medial PFC (BA 9), right medial temporal cortex (BA 28/34), bilateral middle temporal cortex (BA 21) and inferior parietal cortex (BA 40). During retrieval vs. encoding, both groups activated the right lateral occipital cortex (BA 19/37), right DLPFC (BA 9), left anterior-DLPFC (BA 46/10), and bilateral precentral cortex (BA 6) (see Table 4). Figure 2B shows that for both groups, there was greater activation in the left medial PFC (BA9) and left VLPFC (BA47) during encoding vs. retrieval and greater activation in the right DLPFC (BA 9) and left anterior DLPFC (BA 46/10) at retrieval vs. encoding.

LV 5: Easy vs. Hard Retrieval Main Effect

Figure 3 and Table 5 present the whole-brain PLS results for LV 5: brain activity during easy vs. hard retrieval events in both groups. This contrast identified regions differentially activated during correctly retrieved context in the easy (Figure 3A, red represents positive saliences, coloured in red) vs. hard retrieval conditions (Figure 3A, blue represents negative brain saliences). For easy vs. hard retrieval, both groups activated left postcentral cortex (BA 2 and 4). During hard vs. easy events, both groups activated right medial occipital cortex (BA 17) and left DLPFC (BA 46). Figure 3B represents the activation profile for an ROI in the prefrontal

cortex. During easy vs. hard retrieval, both groups activated the left DLPFC (BA 46) in hard vs. easy retrieval tasks.

LV 6: Encoding vs. Retrieval Interaction

Figure 4 and Table 6 present the whole-brain PLS results for LV 6: group differences in brain activity during successful encoding vs. retrieval. Positive saliences (Figure 4A, red regions) were areas that middle-aged adults activated more at retrieval vs. encoding, and young adults activated more at encoding vs. retrieval. Negative saliences (Figure 3a, blue regions) represent the opposite effect. Figure 4B shows that young adults activated left anterior PFC (BA 10) to a greater extent at retrieval vs. encoding.

LV 10: Easy vs. Hard Retrieval Interaction

Figure 5 and Table 7 present the whole-brain PLS results for LV 10: group differences in brain activity during easy vs. hard retrieval. Positive saliences (Figure 5A, red regions) represent regions where middle-aged adults exhibited increased activation during hard vs. easy retrieval events, and young adults exhibited the inverse effect. There were no significant negative salience regions at the thresholds used. Figure 4b shows that middle-aged adults exhibited greater activation in the right VLPFC (BA 47), DLPFC (BA 9), and APFC (BA 10) in hard vs. easy tasks

Linear Regressions

Predictor variables included in the easy and hard PFC models are marked by asterisks in Tables 4 – 7. Mean activity in these PFC ROIs were also plotted in Figures 1 – 4. For LV 1 (encoding vs. retrieval main effect) and LV 6 (encoding vs. retrieval interaction) the PFC ROIs for both encoding and retrieval were included as predictors in the models. For easy accuracy models, only

mean activity during easy retrieval events were included as predictors for ROIs from LV 5 (main effect of difficulty) and LV 10 (group by difficulty interaction). For hard accuracy models only mean activity during hard retrieval events were included as predictors for ROIs from LV5 (main effect of difficulty) and LV10 (group by difficulty interaction). There were 14 predictors variables included in each model overall.

Young Adult Models

A significant Hard Accuracy – PFC Predictor model was identified in young adults ($F(5, 21) = 2.71$, $p < 0.05$, adjusted $R^2 = 0.39$), in which increased retrieval activity in left anterior PFC (LV6, BA 10, standardized b = +.67) and left DLPFC (LV5, BA 46, standardized b = +.48) positively predicted retrieval accuracy on hard context memory tasks; and increased retrieval activity in left medial PFC (LV1, BA 9, standardized b = -.30), left anterior DLPFC (LV1, BA 46/10, standardized b = -.58) and right VLPFC (LV10, BA 47, standardized b = -.34) negatively predicted hard retrieval accuracy. The model for easy accuracy was not significant in young adults. .

Middle Aged Adult Models

In middle aged adults significant results were obtained for the Easy Accuracy – PFC Model ($F(4, 17) = 4.82$, $p < 0.01$, $R^2 = 0.53$). Increased encoding and retrieval activity in left medial BA 9 (LV1; encoding standardized b = +.40; retrieval standardized b = +.19), and increased retrieval activity in left DLPFC (LV5, BA 46; standardized b = +.17) and right anterior PFC (LV 10, BA 10; standardize b = +.10) positively predicted easy retrieval accuracy. The model for hard accuracy was not significant in middle-aged adults

Cortical thickness results

A surface-based GLM analysis revealed significant correlations with cortical thickness and age (Figure 6, Table 8). All areas reported showed significant differences at a significance threshold of $p < 0.001$. Significant cortical thinning was found in the left DLPFC (BA 46, BA9), left VLPFC (BA 47) and the right DLPFC (BA 9).

Linear Regressions

Predictor variables included in the easy and hard PFC models are marked by asterisks in Tables 8. For both easy and hard accuracy models, cortical thickness values (in mm) in the left BA 46, BA 9, and BA 47 and right BA9 were included. There were 4 predictors variables included in each model overall. No significant young or middle-aged adult models of easy or hard accuracy with cortical thickness were found in the ROIs tested.

7. Discussion

Middle-aged adults exhibit deficits in performance on contextual memory tasks along with both structural and function changes in memory-related areas of the brain. More specifically, middle-aged adults show a marked decrease in tasks of temporal context memory, as well as tasks involving a high memory load. Young and middle-aged adults exhibit group similarities in functional activity in the prefrontal cortex at encoding and retrieval and differences only at retrieval. Age-related cortical thinning was also found in corresponding structures in the PFC. The implications of these findings are described below.

Contextual memory decline at middle age

Middle-aged adults showed decreased accuracy on the hard spatial context tasks, and both temporal context tasks compared to young adults. Previous studies have found a similar decline in spatial context memory in middle-aged adults (Cansino et al. 2010, 2012). These

studies utilized 120 stimuli at encoding, making it a high load memory task. Previous studies have found that memory maintenance at higher loads is sensitive to age (Mitchell et al, 2000; Nagel et al, 2010; Cappell et al, 2010). The lack of differences in the spatial easy condition points to the possibility the middle-aged adults retain memory for spatial context at low loads but begin to experience decline in the more demanding high-load memory tasks.

Middle-aged adults also exhibited declines in temporal context memory in both the high and low load conditions. They also performed more poorly on the temporal easy tasks than the spatial hard tasks, revealing they had more difficulty memorizing the temporal than the spatial information. Few studies have compared temporal and spatial context memory, and this is the first study to find that temporal context declines in middle-aged adults. A study by Parkin et al (1995) compared spatial and temporal context memory in young and older adults and older adults demonstrated a decline in performance in temporal memory but not the spatial memory tasks. In addition, they found a correlation between performance on temporal tasks and scores on frontal test (e.g. Wisconsin Card Sorting Task, FAS Word Fluency Test) but no relation between spatial performance and frontal tests. The authors of the study propose that the reason for the observed differences lies in different strategies used in the two task types: memorizing spatial context is often done with reference to one's own location while individuals memorize temporal order by remembering the order of an object with reference to another object. Older adults have an increased tendency to process memories with reference to themselves (Kensinger and Schacter, 2008). The self-referential nature of spatial context memory may result in the overall better memory (in both young and middle-aged adults) and the longer preservation with age. Conversely, the observed temporal context deficits at middle age suggest that middle-aged adults also rely on self-referential processing in memory task.

Middle-aged adults did not exhibit lower RT than young adults in any of the memory tasks. Studies of cognitive aging and memory (Salthouse 1996) have found that older adults exhibit reduced processing speed of cognitive operations with age, which has been attributed to loss in white matter integrity in the frontal lobes with age (Madden et al, 2009). However, the preservation of response speed suggests that the neural mechanisms that mediate processing speed are preserved at middle age.

Similarities in memory-related activation in the prefrontal cortex

Studies of neural activation and cognitive aging have found increases in default mode (i.e. medial PFC) and decreases in task-related regions (i.e. DLPFC) during recognition memory tasks (Grady et al, 2006). The current study found similar encoding-related activations in young and middle-aged adults. The observed group similarities in superior and medial PFC activation at encoding were consistent with the findings of Park et al (2013) where group differences in activity were not apparent between young and middle-aged adults, but increases were found in middle-aged vs. older adults.

Previous studies have found increases in the left DLPFC with working memory load (Nagel, Preuschhof et al, 2011) and with more demanding retrieval tasks where more detailed, deliberative analysis of activated information or maintenance of information is needed (Nolde et al, 1998). Similar activations in the PFC, namely in the VLPFC and DLPFC have been found for working memory and episodic memory (Ranganath et al 2003). Consistent with these studies, we see an increase in left DLPFC activity in hard (high load) tasks. Left DLPFC activity differentially predicted accuracy in the two groups: it predicted accuracy on hard tasks in young adults and accuracy on easy tasks in middle-aged adults. Taken together, these results suggest that increased left DLPFC reflected the increased processing needed for the more demanding

high load task. However, this activity did not contribute to performance on high load tasks in middle-aged adults. Over-activation of the left DLPFC has previously been attributed to neural inefficiency (Morcom, et al 2007) and compensation for deficits in activation; (Cabeza et al, 2002; Kalpouzos et al, 2011). Studies have described the age-related over-activation in the DLPFC during the performance of working memory tasks as being due to older adults relying more on executive processing (Reuter-Lorenz et al, 2000; Cabeza et al, 2002; Cappell et al, 2010) potentially due to the decline in storage capacity. It is possible that in middle-aged adults, functional changes are beginning to occur in the DLPFC that hinders performance, but that they do not display compensation-related over-activation until later in life.

The medial PFC shows increased activity during self-referential encoding tasks (Macrae, 2004) and has previously been found to show increased activity with age (Grady et al., 2006, Kennedy et al., 2012, Park et al., 2013). Increased activity in the medial PFC has been associated with better memory performance on self-referential memory tasks in both young and older adults (Leshikar and Duarte 2013, Maillet and Rajah, 2014). Additionally focusing on social information has shown to provide a source memory benefit for older adults (Rahhal, 2002). In the current study, both young and middle-aged adults similarly used self-referential processing while making pleasantness judgements for the face stimuli at encoding. In middle-aged adults, the activity in the medial PFC positively predicted accuracy on easy tasks, suggesting that they relied more heavily on self-referential processing to help their performance. The pleasantness judgements may not have always led to successful encoding, as increased medial PFC activity negatively predicting accuracy on hard tasks for young adults. In the young adult group, increased retrieval activity in the left medial PFC was negatively predictive of success on hard tasks. Self-referential encoding has been shown to be detrimental to retrieval accuracy on more

attention-demanding memory tasks (Kim et al, 2011). Increasing self-referential processing may have helped middle-aged adults in the easy tasks, but this may have contributed to their decline in performance on the hard tasks.

Age-related functional differences in the prefrontal cortex

At encoding, both young and middle-aged adults displayed similar activation in the left anterior PFC, but only young adults displayed increased activation in left anterior PFC (APFC) at retrieval vs. encoding. This region was also found to be positively correlated with accuracy on hard retrieval tasks in young but not middle-aged adults, suggesting that the increased APFC activity may have aided young adults in processing contextual features. The decreased APFC activity at retrieval may explain the behavioural deficits in middle-aged adults, which may have been compensated by increased retrieval activity in other PFC regions such as the medial PFC (discussed above) or the right VLPFC, DLPFC and APFC (discussed below). It is also possible that middle-aged adults relied more heavily on self-referential processing (as discussed above with respect to the medial PFC) rather than contextual details, making it more difficult to recall these details at retrieval.

At retrieval, the right VLPFC, DLPFC, and APFC showed similar activations in easy and hard tasks in young adults, but middle-aged adults increased activation in these areas only for hard tasks. These areas may have been over-recruited to compensate for reductions in other regions (i.e. the left APFC). Increased activity in the right anterior PFC positively predicted accuracy on easy tasks for middle-aged adults provides additional support that the over-activation was compensatory. The DLPFC is one of the sites where researchers have found the most prominent activation differences with age (Rossi et al, 2004; Cappell et al, 2010; Rajah et al,

2011) and is a region that is critical for executive functions such as manipulating and monitoring information. Additionally, right VLPFC activity negatively predicted accuracy on hard tasks in young adults, suggesting that the over-recruitment of this area may have caused a negative effect on performance in middle-aged adults.

Age-related structural changes and their relation to function

Previous studies have found that the prefrontal cortex is one of the first regions to display age-related decline (Fjell et al, 2009; Salat et al, 2004; Raz et al, 1997). As expected, the most prevalent thinning occurred in the prefrontal cortices, namely in the left DLPFC, left VLPFC, and right DLPFC.

Over-activation in seniors is often found in areas of the prefrontal cortex that approximately mirror the sites that are activated in young adults but in the opposite hemisphere (Cabeza, 2002; Reuter-Lorenz, 2000). This bilateral activation in older adults has been previously described as functional compensation for age-related loss in structural and functional integrity (Reuter-Lorenz & Cappell, 2008). As such, the increased activation seen in the areas of the right DLPFC and right VLPFC may have been attempted compensation for volumetric loss in the left DLPFC and left VLPFC.

No significant relationships between prefrontal cortical thickness and behaviour were found, meaning further analysis is needed to determine whether the loss in structural integrity led to volume loss. One potential reason for lack of a significant effect may have been the small sample size – previous studies assessing cortical thickness have used much larger samples (>100); the current study had a sample of less than 50 subjects. Currently, we can only draw

preliminary conclusions regarding potential compensation (as described earlier) or neural inefficiencies based on overactivtion of prefrontal areas in more demanding tasks at middle-age.

8. Limitations

There were a few limitations to the current study. Functionally, the major limitation was that no differences in activity were found between spatial and temporal context memory. Therefore it was not possible to assess the functional changes that led to the behavioural differences in spatial and temporal memory between young and middle-aged adults.

Structurally, there were three major methodological considerations. First, a larger sample size was needed to find significant differences after multiple comparisons for the cortical thickness analysis. Previous studies assessing cortical thickness change in age have used samples sizes that were > 100 (Raz et al, 1997; Salat et al, 2004; Fjell et al, 2009). There were less than 50 subjects in the current study. As a result, an uncorrected P-value was used in the analysis ($p < 0.001$).

Another limitation was that cross-sectional data, rather than longitudinal data, was used to compare structural changes with age. Therefore, the results may have been subject to cohort effects as well as effects of interindividual variability. In addition, age-related changes in T1-weighted MR signal poses a potential confound when comparing structural changes in young and middle-aged adults (Davatizkos & Resnick, 2002). In the current study, motion correction and signal intensity normalisation were utilized in order to mitigate these effects (Salat et al, 2004).

9. Conclusion

The current study shows that episodic memory decline is apparent by midlife. Middle-aged adults experience changes in accuracy but not reaction time on context memory tasks.Encoding-

related activity in the left medial PFC and left VLPFC and retrieval-related activity in the DLPFC remained intact in middle-aged adults compared to young adults. Age-related decline in the left anterior PFC activity were found at retrieval and age-related increased in activity were found in right PFC during hard vs. easy retrieval events. The cortical thinning was found in the bilateral DLPFC and left VLPFC. Overall, increased activity in the right PFC may reflect either neural inefficiencies or attempted compensatory activity. Further studies are needed to determine the exact mechanisms in which the age-related changes are occurring, and the specific effects of each change on memory. Understanding the changes that occur in the brain with healthy aging can help identify potential markers for early detection of pathological aging and increase the quality of life of elderly who suffer from losses in episodic memory.

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Table 1 – Mean Education and Neuropsychological Results

Group		Education (years)	MMSE	BDI	NART	LFCVLT	LCRCVLT	RGCVLT
Young adults	Mean	16.44	29.74	3.33	40.74	13.78*	13.81	15.37
	S.E.	0.27	0.53	0.66	1.02	0.35	0.34	0.15
Middle-aged adults	Mean	15.77	29.59	4.32	41.27	12.40*	13.05	15.32
	S.E.	0.30	0.73	1.01	1.22	0.56	0.49	0.17

Note: This table presents the group means and standard errors (S.E.) for education and other psychological measures taken. MMSE = mini-mental status examination; BDI = Beck Depression Inventory; NART = American National Adult Reading Test; LFCVLT = CVLT, long-from free recall; LCRCVLT = CVLT, long-form category assisted recall; RGCVLT = CVLT, long-term recognition. Significant differences are highlighted with asterisks.

Table 2 – Mean Retrieval Accuracy and Reaction Time

Group		Spatial Easy	Spatial Hard	Temporal Easy	Temporal Hard
Young Adults	Mean RT (msec)	2271.64 (95.45)	2385.61 (92.77)	2645.19 (102.60)	2810.47 (109.46)
	Mean Accuracy	0.89 (0.02)	0.89* (0.02)	0.77* (0.02)	0.69* (0.02)
Middle-aged Adults	Mean RT (msec)	2455.24 (89.86)	2592.56 (83.72)	2856.67 (97.94)	2963.60 (97.03)
	Mean Accuracy	0.87 (0.02)	0.81* (0.03)	0.65* (0.03)	0.58* (0.03)

Note: Accuracy values are shown as proportion correct per task type with standard error (SE). Reaction time values are shown in milliseconds (msec) per task type with SE. Significant differences are highlighted with asterisks.

Table 3 – Contrasts for the Non-Rotated PLS Analysis

Contrast Number	Contrast	Event-types
Group similarities		
1	Encoding vs. Retrieval Events Main effect	eSE, eSH, eTE, eTH vs. rSE, rTE, rSH, rTH
2	Spatial vs. Temporal Encoding Events Main effect	eSE, eSH vs. eTE, eTH
3	Spatial vs. Temporal Retrieval Events Main effect	rSE, rSH vs. rTE, rTH
4	Easy vs. Hard Encoding Events Main effect	eSE, eTE vs. eSH, eTH
5	Easy vs. Hard Retrieval Events Main effect	rSE, rSE vs. rSH, rTH
Group differences		
6	Encoding vs. Retrieval Events, Group Interaction	Young: eSE, eSH, eTE, eTH vs. rSE, rSH, rTE, rTH Middle aged: rSE, rTE, rSH, rTH vs. eSE, eTE, eSH, eTH
7	Spatial vs. Temporal Encoding Events, Group interaction	Young: eSE, eSH vs. eTE, eTH Middle aged: eTE, eTH vs. eSE, eSH
8	Spatial vs. Temporal Retrieval Events, Group interaction	Young: rSE, rSH vs. rTE, rTH; Middle aged: rTE, rTH vs. rSE, rSH
9	Easy vs. Hard Encoding Events, Group interaction	Young: eSE, eTE vs. eSH, eTH; Middle aged: eSH, eTH vs. eSE, eSE
10	Easy vs. Hard Retrieval Events, Group interaction	Young: rSE, rTE vs. rSH, rTH; Middle aged: rSH, rTH vs. rSE, rSE
11	Young vs. Middle Aged Group Main effect	All Event-types in Young vs. All Event-types in middle-aged

Table 4 – Local maxima for LV1 (Encoding vs. Retrieval Main Effect)

Temporal Lag	Bootstrap ratio	Spatial extent	Talairach coordinates x	y	z	HEM	Gyral location	Brodmann area
Encoding vs. Retrieval								
2-3-4	11.96	941	-9	-96	9	Left	Cuneus	17
2-3	9.86	930	-57	-53	31	Left	Supramarginal Gyrus	40/39
2-3	8.07	1128	-5	45	30	Left	Medial Frontal Gyrus	9*
2	7.80	145	-6	-53	68	Left	Precuneus	7
2-4	7.36	200	-8	33	0	Left	Anterior Cingulate	24
4	6.50	416	-60	-42	-4	Left	Middle Temporal Gyrus	21
2-3-4	6.07	258	-49	25	2	Left	Inferior Frontal Gyrus	47*
2-4	5.18	27	-39	17	48	Left	Superior Frontal Gyrus	8
2	5.06	15	-23	-3	-22	Left	Amygdala	
3	4.92	44	-49	2	-29	Left	Middle Temporal Gyrus	21
2	4.88	21	-46	-14	53	Left	Precentral Gyrus	4
2	4.56	46	-2	-4	69	Left	Superior Frontal Gyrus	6
2	4.29	22	-41	17	-34	Left	Superior Temporal Gyrus	38
4	4.01	11	-20	20	53	Left	Middle Frontal Gyrus	6
3	3.69	15	-5	-20	35	Left	Cingulate Gyrus	24
2	9.14	1419	58	-27	28	Right	Inferior Parietal Lobule	40
3-4	9.08	1110	58	-50	29	Right	Supramarginal Gyrus	40/39

2-3	6.28	37	39	20	47	Right	Middle/Superior Frontal Gyrus	8
3-4	6.24	56	48	13	-30	Right	Superior Temporal Gyrus	38
2-3	4.61	83	13	39	44	Right	Superior Frontal Gyrus	8
4	4.44	50	66	-36	2	Right	Middle Temporal Gyrus	21
2	4.22	17	18	4	-20	Right	Uncus	28/34
4	3.71	15	21	-45	22	Right	Cingulate Gyrus	31
Retrieval vs. Encoding								
2-3	-11.03	995	-27	17	2	Left	Claustrum	
4	-10.23	1222	-38	-48	-23	Left	Cerebellum/Occipital gyrus	
2	-7.90	115	-38	7	30	Left	Inferior Frontal Gyrus	44/6
3	-7.55	181	-38	3	29	Left	Precentral Gyrus	6
4	-6.99	188	-27	17	2	Left	Claustrum	
2-4	-5.99	50	-28	-14	49	Left	Precentral Gyrus	6
4	-5.74	46	-38	-6	7	Left	Insula	13
2	-5.61	48	-9	1	51	Left	Medial Frontal Gyrus	6
2-3-4	-5.46	44	-42	51	8	Left	Middle/Superior Frontal Gyrus	46/10*
4	-14.56	1489	40	-76	-9	Right	Occipital/Fusiform gyrus	19/37
4	-7.82	207	29	21	0	Right	Claustrum	
2-4	-7.71	220	51	22	32	Right	Middle Frontal Gyrus	9*
4	-5.54	107	10	-13	7	Right	Thalamus	
4	-4.35	12	36	-3	12	Right	Claustrum	

2-4	-4.25	16	28	-18	53	Right	Precentral Gyrus	6
4	-3.75	10	39	-34	63	Right	Postcentral Gyrus	3

Note for Tables 4-7: Temporal lag represents the time after event onset, when a cluster of voxels exhibited a contrast effect of interest. The bootstrap ratio threshold was set to ± > 3.275. The spatial extent refers to the total number of voxels in the voxel cluster (threshold = 10). The stereotaxic coordinates are measured in millimeters. The gyral locations and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988a,b). HEM: Cerebral hemisphere in which the activation occurred. Regions marked with * were ROIs for which: i) mean activity was extracted and plotted in a bar graph and ii) region-specific brain-behavior correlations were conducted.

Table 5 – Local maxima for LV 5 (Easy vs. Hard Retrieval Main Effect)

Temporal Lag	Bootstrap ratio	Spatial extent	Talairach coordinates x	y	z	HEM	Gyral location	Brodmann area
Easy vs. Hard								
4	5.00	59	-50	-29	55	Left	Postcentral Gyrus	2
2-3	4.52	81	-35	-26	59	Left	Precentral Gyrus	4
Hard vs. Easy								
4	-6.10	75	-39	2	47	Left	Middle Frontal Gyrus	6/8
3-4	-4.33	66	-31	35	14	Left	Middle Frontal Gyrus	46*
2-3-4	-8.77	533	13	-92	3	Right	Cuneus	17

Table 6 – Local maxima for LV 6 (Encoding vs. Retrieval, Group Interaction Effect)

Temporal Lag	Bootstrap ratio	Spatial extent	Talairach coordinates x	y	z	HEM	Gyral location	Brodmann area
Young Encoding vs. Retrieval, MA Retrieval vs. Encoding								
3	5.11	13	-53	-70	8	Left	Middle Occipital Gyrus	19
2	4.29	10	-49	11	-10	Left	Superior Temporal Gyrus	38
2	4.26	20	35	-63	57	Right	Superior Parietal Lobule	7
Young Retrieval vs. Encoding, MA Encoding vs. Retrieval								
2	-5.12	24	-39	-22	59	Left	Postcentral Gyrus	4
4	-4.92	18	-27	-92	9	Left	Middle Occipital Gyrus	18
4	-4.22	14	-16	54	16	Left	Anterior Medial frontal gyrus	10*
2	-3.73	10	46	-22	53	Right	Postcentral Gyrus	3

Table 7 – Local maxima for LV 10 (Easy vs. Hard Retrieval, Group Interaction Effect)

Temporal Lag	Bootstrap ratio	Spatial extent	Talairach coordinates x	y	z	HEM	Gyral location	Brodmann area
Young Easy vs. Hard, MA Hard vs. Easy								
3	5.96	113	-23	24	10	Left	Claustrum	
2-3	4.99	110	-31	-87	-12	Left	Inferior Occipital Gyrus	18*
3-4	4.83	128	-35	29	39	Left	Middle Frontal Gyrus	8
4	4.67	23	-42	-18	-20	Left	Sub-Gyral	20
3	4.37	32	-17	4	62	Left	Medial Frontal Gyrus	6
3	4.13	12	-49	-49	-12	Left	Fusiform Gyrus	37
3	3.74	34	-20	-65	37	Left	Precuneus	7
3	5.09	49	36	37	-6	Right	Inferior Frontal Gyrus	47*
4	5.01	44	47	-18	-22	Right	Inferior Temporal Gyrus	20
3	4.76	117	10	21	42	Right	Cingulate Gyrus	32
3	4.73	26	17	9	9	Right	Putamen	
3	4.72	23	66	-43	-2	Right	Middle Temporal Gyrus	21
3-4	4.71	41	29	48	-5	Right	Superior Frontal Gyrus	10*
4	4.67	5	36	-10	-28	Right	Uncus	20
3-4	4.44	18	28	12	56	Right	Middle Frontal Gyrus	6
3	4.23	106	13	-73	44	Right	Precuneus	7

3	4.08	23	10	23	17	Right	Anterior Cingulate	24
2	3.85	18	28	-72	30	Right	Precuneus	7/19
3	3.82	28	32	36	37	Right	Middle Frontal Gyrus	9*

Table 8 – Cortical thickness

			Talairach Coordinates				
Log(10)p	HEM	Size (mm^2)	x	y	z	Gyral location	Brodmann Area
-4.782	Left	180.17	-17.7	-69.6	1.1	Lingual Gyrus	18
-4.5423	Left	46.88	-31.2	29.4	6.3	Inferior Frontal Gyrus	45
-3.9076	Left	155.03	-41	15.4	7.2	Precentral Gyrus	44
-3.8635	Left	50.08	-12.3	43.3	42.3	Superior Frontal Gyrus	8
-3.7383	Left	57.83	-39.9	29.6	18.5	Middle Frontal Gyrus	46*
-3.6107	Left	100.92	-13.2	31.5	26	Cingulate Gyrus	32
-3.5812	Left	22.22	-37.2	-27.7	5	Superior Temporal Gyrus	13
-3.4851	Left	19.55	-47.4	-19.3	-0.5	Superior Temporal Gyrus	22
-3.4455	Left	21.2	-36	1.8	27.3	Precentral Gyrus	6
-3.4178	Left	46.02	-7.8	43.2	-15.2	Medial Frontal Gyrus	11
-3.3493	Left	15.2	-18.3	21.8	56.5	Superior Frontal Gyrus	6
-3.297	Left	16.5	-43.2	-40.7	18.6	Insula	13
-3.1906	Left	10.57	-33.5	12.5	27.9	Middle Frontal Gyrus	9*
-3.1358	Left	12.19	-43.7	39.6	-10	Middle Frontal Gyrus	47*
-3.08	Left	3.81	-6	33.5	-4.9	Anterior Cingulate	32
-3.0657	Left	4.7	-45.1	9	3.5	Insula	13
-4.7865	Right	99.14	54.1	26.7	7.6	Inferior Frontal Gyrus	45
-4.1405	Right	315.65	7.1	29.3	-9.2	Anterior Cingulate	32
-3.9461	Right	139.83	15.5	53.2	25.7	Superior Frontal Gyrus	9*
-3.7904	Right	88.19	43.6	35.9	3.8	Inferior Frontal Gyrus	45
-3.7861	Right	45.94	46.1	-18.8	-4.4	Superior Temporal Gyrus	22
-3.5766	Right	16.67	36.5	-30	39.9	Inferior Parietal Lobule	40
-3.2135	Right	6.65	37.8	-26.1	2.7	Insula	13
-3.1324	Right	3.62	44.9	-26.5	-4.6	Superior Temporal Gyrus	22
-3.0822	Right	4.19	40.8	-4.2	18.2	Insula	13

Note: The gyral locations and Brodmann areas (BAs) were determined by referring to Talairach and Tournoux (1988a,b). HEM: Cerebral hemisphere in which the activation occurred. Regions marked with * were ROIs in the prefrontal cortex.

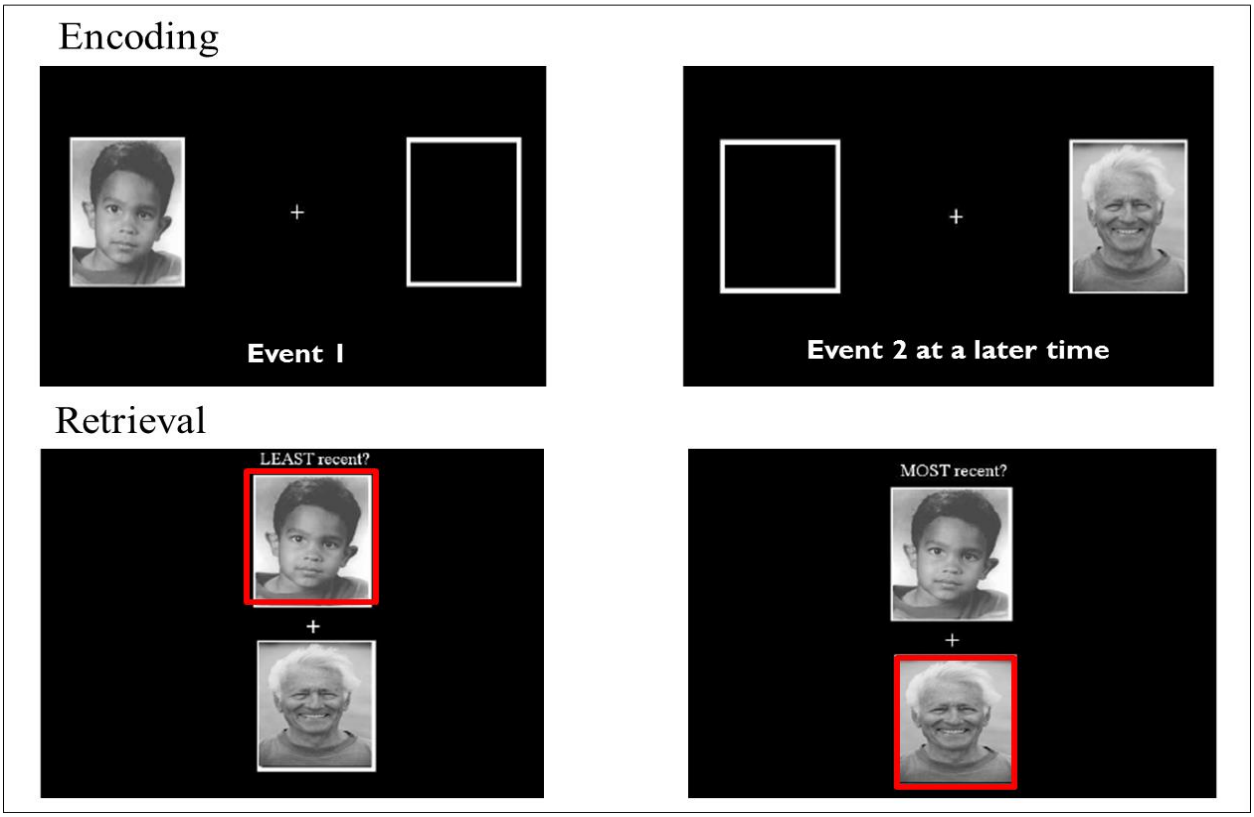

Figure 1) Task paradigm. At encoding, stimuli were presented at either the left or right of the screen and participants made subjective evaluations about the faces (pleasant or neutral). At retrieval, two faces were presented at a time to the top and bottom of the screen, and subjects indicated which face they saw to the left or right or least or more recently depending on the task condition.

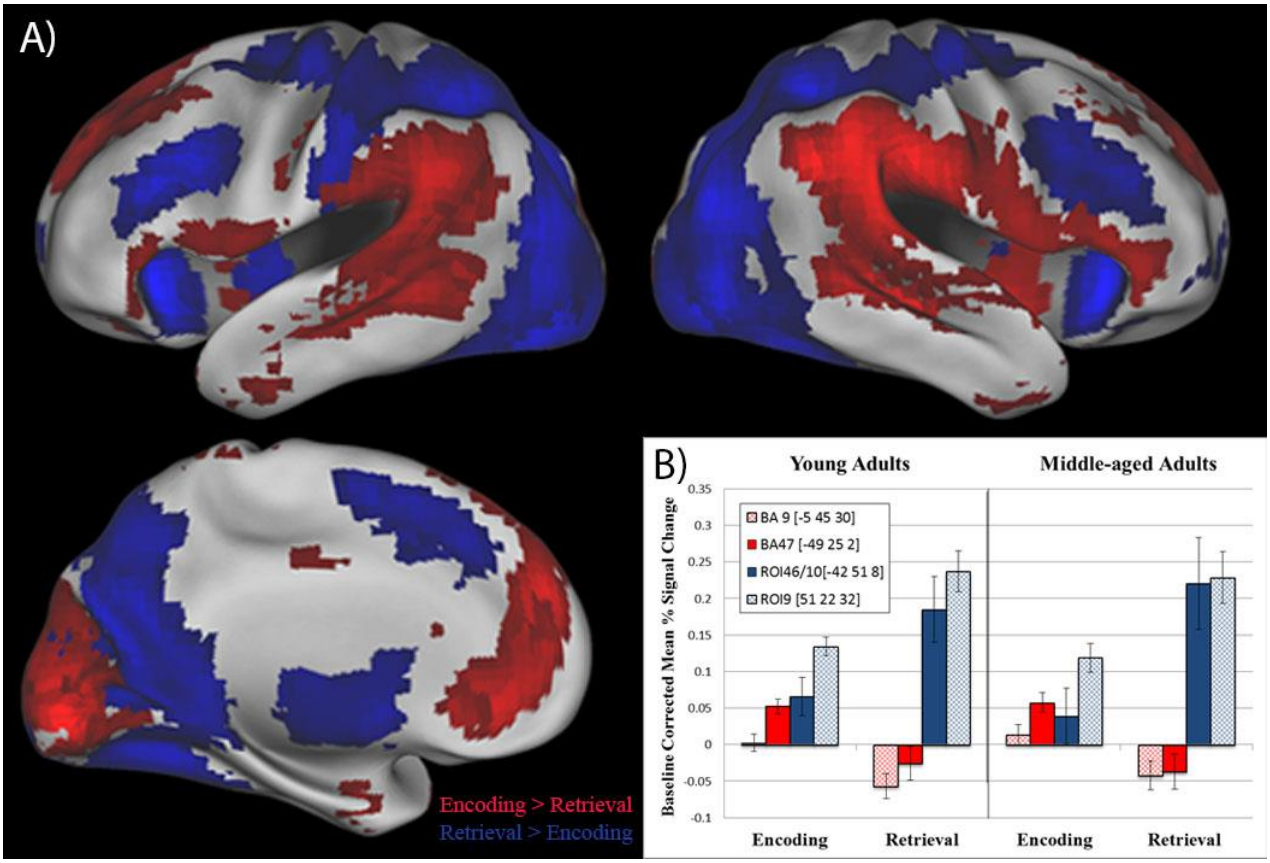

Figure 2) Latent Variable 1. A) Singular image for the encoding vs. retrieval main effect at a bootstrap ratio of ±3.275 ($p < 0.001$) for activations at time lags 2-4. Red regions are positively related to the main effect and blue regions are negatively related to the main effect. **B)** Bar graphs representing mean activation for young and middle-aged adults with standard error bars in regions of interest that exhibited an encoding vs. retrieval main effect.

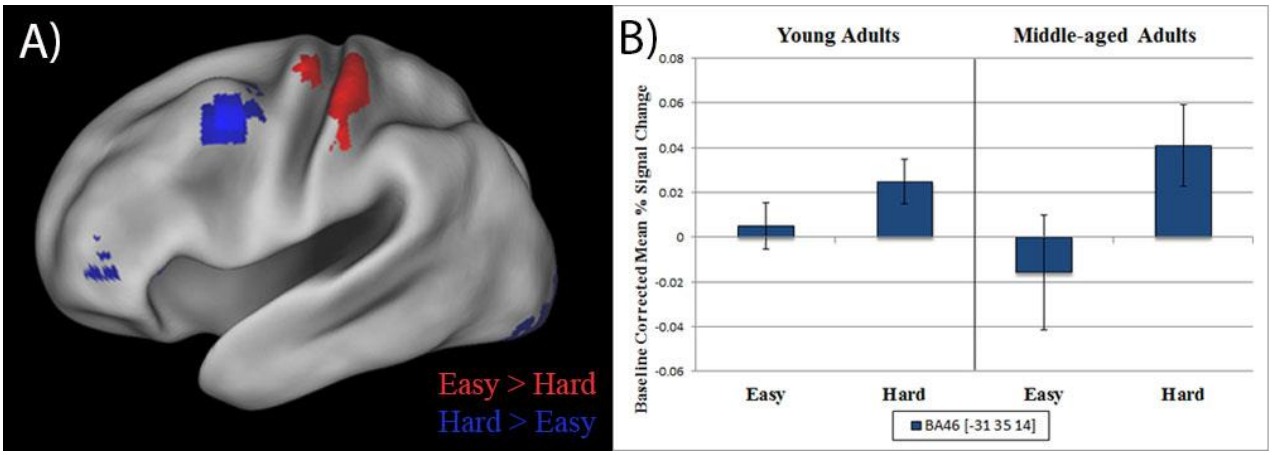

Figure 3) Latent Variable 5. A) Singular image for the easy vs. hard retrieval main effect at a bootstrap ratio of ±3.275 ($p < 0.001$) for activations at time lags 2-4. Red regions are positively related to the main effect and blue regions are negatively related to the main effect. **B)** Bar graphs representing mean activation for young and middle-aged adults with standard error bars in regions of interest that exhibited an easy vs. hard retrieval main effect.

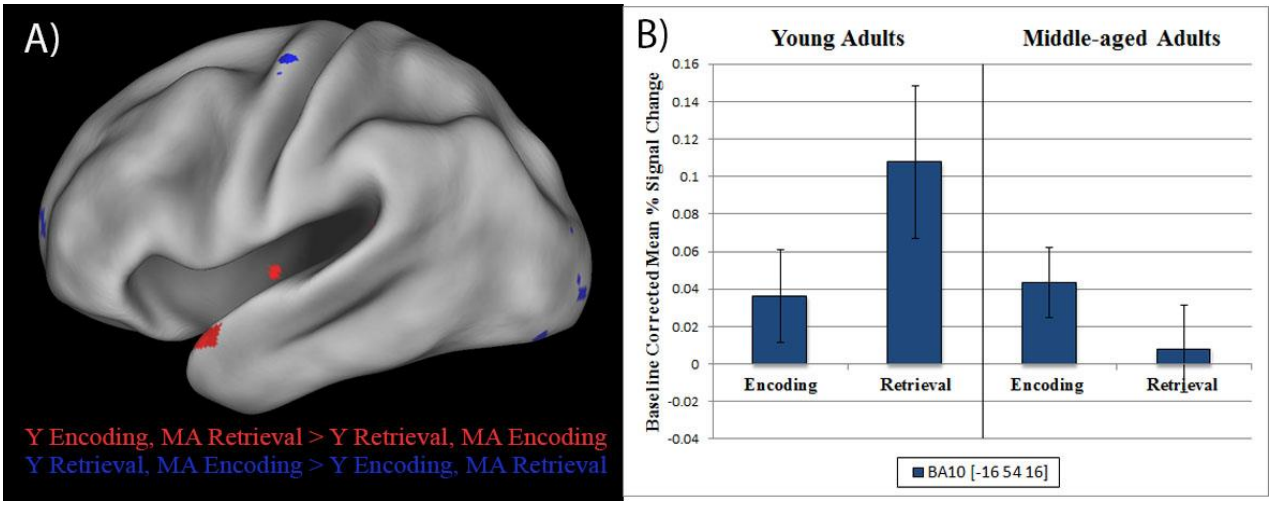

Figure 4) Latent Variable 6. A) Singular image for the encoding vs. retrieval interaction at a bootstrap ratio of ±3.275 ($p < 0.001$) for activations at time lags 2-4. Red regions are positively related to the main effect and blue regions are negatively related to the main effect. **B)** Bar graphs representing mean activation for young and middle-aged adults with standard error bars in regions of interest that exhibited an encoding vs. retrieval interaction.

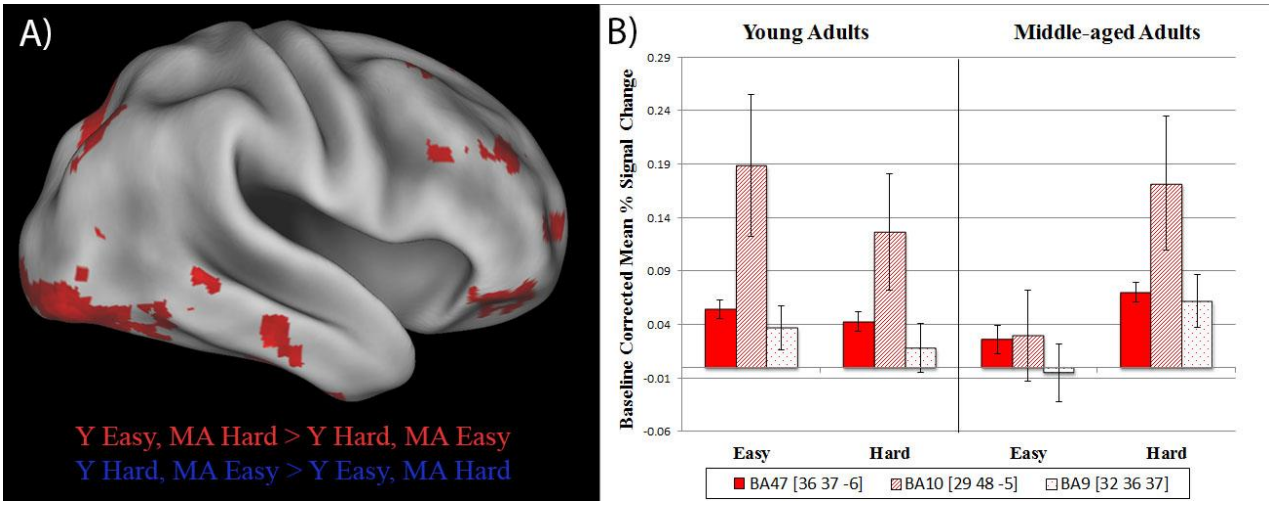

Figure 5) Latent Variable 10. A) Singular image for the easy vs. hard retrieval interaction at a bootstrap ratio of ±3.275 ($p < 0.001$) for activations at time lags 2-4. Red regions are positively related to the main effect and blue regions are negatively related to the main effect. **B)** Bar graphs representing mean activation for young and middle-aged adults with standard error bars in regions of interest that exhibited an easy vs. hard retrieval interaction.

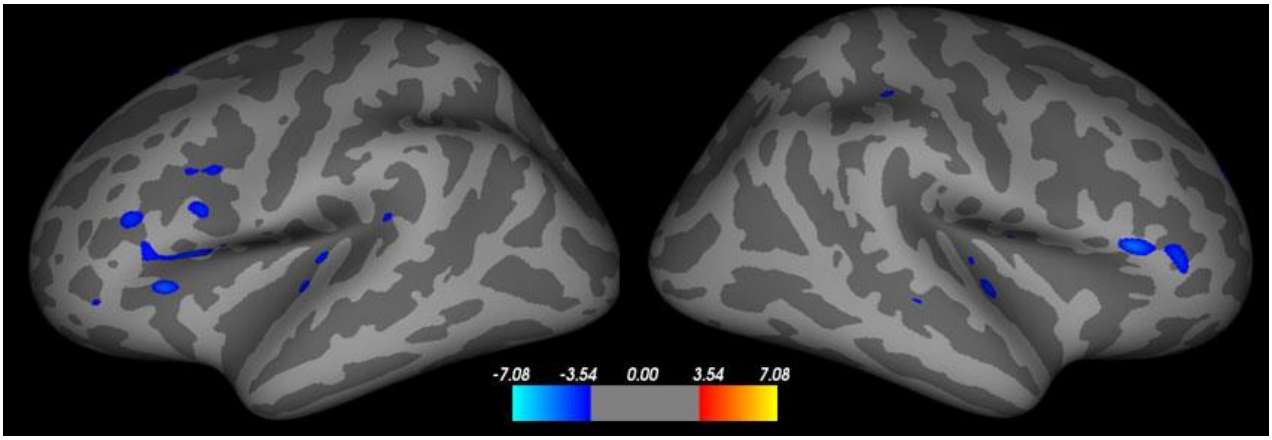

Figure 6) Cortical thickness. Surface based vertex-wise GLM maps showing correlations between age and thickness. Blue represents areas that were negatively correlated with age. No regions were found to be positively correlated with age at the thresholds tested.