Age- and reserve-related increases in fronto-parietal and anterior hippocampal activity during episodic encoding predict subsequent memory

Running Head: The effect of reserve on memory and brain aging across the adult lifespan.

Abdelhalim Elshiekh[1], Sivaniya Subramaniapillai[2], Sricharana Rajagopal[3], Stamatoula. Pasvanis[3], Elizabeth Ankudowich[1], and M. Natasha Rajah[3,4]

1. Integrated Program in Neuroscience, McGill University, Montreal, QC, Canada
2. Department of Psychology, McGill University, Montreal, QC, Canada
3. Brain Imaging Centre, Douglas Institute Research Centre, Verdun, QC, Canada
4. Department of Psychiatry, Faculty of Medicine, McGill University, Montreal, QC Canada

Corresponding Author:
M. Natasha Rajah, Ph.D.
Room 2114, CIC Pavilion
Douglas Institute Research Centre
6875 LaSalle Boulevard
Verdun, Quebec H4H 1R3
Email: maria.rajah@mcgill.ca

Abstract

Remembering associations between encoded items and their contextual setting is a feature of episodic memory. Although this ability deteriorates with age in general, there is substantial variability in how older individuals perform on episodic memory tasks. This variability may stem from genetic and/or environmental factors related to reserve, allowing some individuals to compensate for age-related decline through differential recruitment of brain regions. In this fMRI study, we tested predictions related to reserve and compensation in a large adult lifespan sample (N=154). We used multivariate Behaviour Partial Least Squares (B-PLS) analysis to examine how age, retrieval accuracy, and a proxy measure of reserve, impacted brain activity patterns during spatial and temporal context encoding and retrieval. Reserve modulated age-related compensatory brain responses in ventral visual, temporal, and fronto-parietal regions during memory encoding as a function of task demands. Activity in inferior parietal, medial temporal, and ventral visual regions were strongly impacted by age at encoding and retrieval, but were also related to individual differences in reserve. Our findings are consistent with the concepts of reserve and compensation and suggest that reserve may mitigate age-related decline by modulating compensatory brain responses in the aging brain.

1. Introduction

In everyday life, we are commonly faced with instances where we need to remember past events that occurred at a specific time and place, such as remembering where we parked our vehicle after a shopping trip. This type of long term memory for personally experienced events is referred to as episodic memory (Tulving, 2002). Episodic memory contains information about the content of past events, or item memory, and the surrounding details, such as the *when* and *where* of an event; commonly referred to as context/source memory (Johnson, Hashtroudi, & Lindsay, 1993; Tulving, 2002). In general, research has found that healthy aging is associated with greater declines in context memory, compared to item memory (Spencer & Raz, 1995). However, most cognitive aging studies of context memory have focused on mean changes in memory performance with age, and thus assume that older adults (OA) are a homogenous group (Anderson et al., 2008; Cansino et al., 2013; Hashtroudi, Johnson, & Chrosniak, 1989; McIntyre & Craik, 1987; Wegesin, Jacobs, Zubin, Ventura, & Stern, 2000). Yet, a growing body of evidence suggests that episodic memory performance is highly heterogeneous among individuals, and that this variance is typically even higher in OA (Christensen et al., 1999; Lindenberger & Ghisletta, 2009; Morse, 1993; Nilsson et al., 1997; Spreng, Wojtowicz, & Grady, 2010; Wilson et al., 2002; see Tucker-Drob & Salthouse, 2013 for a review). As such, there is a portion of OA who do not exhibit context memory declines with age, compared to young adults (YA).

Several neuroimaging studies have examined the functional neural correlates that differentiate OA who perform similarly to YA on episodic memory tasks, compared to OA who exhibit the more traditional age-related episodic memory decline (Cabeza, Anderson, Locantore, & McIntosh, 2002; Duarte, Henson, & Graham, 2008; Meusel, Grady, Ebert, & Anderson,

2017). For example, Cabeza et al. (2002) compared brain activity in YA and OA, using Positron Emission Tomography (PET) during paired associate cued recall and context memory tasks. The OA were divided into high- and low-performance groups, based on their scores on a composite measure of frontal lobe function (Glisky, Polster, & Routhieaux, 1995). High-performing older adults (High-OA) showed matched performance to YA on both memory tasks, while low-performing older adults (Low-OA) were impaired on both tasks compared to YA. The PET results indicated that Low-OA showed greater right lateralized prefrontal cortex (PFC) activity during context memory, compared to the recall task. Moreover, this pattern of brain activity was similar to that observed in YA. In contrast, High-OA showed bilateral PFC engagement. This pattern of bilateral PFC activity in the High-OA group was interpreted as reflecting successful *functional compensation* in the aging brain, for underlying age-related deficits in PFC structural integrity (Cabeza & Dennis, 2013), or processing deficits in posterior cortical regions (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Grady et al., 1994). Therefore, increased variability in memory performance with advanced age may in part be related to variability in OA's ability to engage neural compensatory mechanisms in response to structure/functional decline in other brain regions or networks.

The ability of some OA to perform as well as YA on memory tasks may also be explained by individual differences in *reserve* (Stern, 2002, 2012). According to the reserve hypothesis, individual differences in genetics, environment and life experiences, impact the accrual of neural resources that help counter the effects of age-related neural decline on cognitive function (Cabeza et al., 2018). Thus, individuals with higher reserve would be better able to stave off the negative impacts of age-related neural decline, than individuals with lower reserve. Some of the factors that promote reserve include education, intelligence, participation in leisure

activities, and occupational complexity. These variables are typically used as indirect proxy measures for reserve, and cross-sectional studies indicate that older adults who have high levels of these proxy measures of reserve, exhibit better episodic memory performance (Angel, Fay, Bouazzaoui, Baudouin, & Isingrini, 2010; Lachman, Agrigoroaei, Murphy, & Tun, 2010). Thus, increased variability in memory performance with advanced age may be related to individual differences in reserve, since the benefits of reserve become more noticeable when neural decline arises (Barulli & Stern, 2013; Cabeza et al., 2018; Stern, 2002, 2012; Tucker & Stern, 2011).

Consistent with this hypothesis, previous studies have shown differential recruitment of brain networks in older adults with high, compared to lower levels of reserve (Stern, 2012). For example, in an fMRI study, Springer et al. (2005) investigated the relationship between whole brain patterns of activity and years of education during episodic encoding and recognition in a group of YA and OA. In YA, they found that education and memory performance was positively correlated with activity in medial temporal, ventral visual and parietal cortices, and a negative correlated with activity in prefrontal cortex (PFC). In OA, higher education was related to increased activity in bilateral PFC and right parietal cortex; however, this pattern of brain activity was not directly correlated with better memory performance in OA. Given that age-related increases in PFC activity have been associated with both greater education (a proxy measure of reserve) and functional compensation, Springer et al (2005) concluded that older adults with greater reserve may be more able to employ compensatory responses when task demands are high. However, as noted in Cabeza et al. (2018), whereas reserve is hypothesized to be trait-like and impact task-general alterations in brain activity with age, compensation is hypothesized to be task-specific and should correlated with task performance. Therefore, the

relationship between reserve-related increases in PFC activity in OA and compensation may be indirect.

In addition to reserve and compensation, individual differences in brain maintenance also contribute to the increased variability in memory performance observed in old age (Lars Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012). According to the brain maintenance concept, individual differences in the slope of age-related brain changes and pathology may result in some OA exhibiting negligible brain changes with age (maintainers), and others exhibiting steeper age-related change (decliners). In other words, brain maintenance postulates that High-OA could be individuals who were also high-performing as young adults (High-YA), and maintained this level of high-functioning into later life (maintainers). In contrast, Low-OA may either be: a) individuals who were low-performing as young adults (Low-YA), and maintained this level of low-functioning into later life (maintainers), or; b) individuals who were low- or high-performing as YA, and exhibited marked declines in brain and cognitive abilities in late life (decliners). From a clinical perspective, it would be important to dissociate these two types of Low-OA, since the former may still be considered to be aging successfully, while the latter may be at greater risk of developing dementia (Wilson, Leurgans, Boyle, Schneider, & Bennett, 2010).

Support for brain maintenance is mostly provided by longitudinal studies showing minimal changes in brain integrity with time in some OA (e.g., Fjell et al., 2009; Nyberg et al., 2010), despite the general consensus that aging is associated with declines in structural brain integrity (Raz et al., 2005, 2012; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010). However, studies utilizing cross-sectional designs can also provide support for brain maintenance. For example, Nagel et al. (2009) examined load-dependant modulation of the

BOLD signal in YA and OA during a spatial working memory task. Initial results revealed an age-related reduction in BOLD signal responsivity to increasing spatial working memory load. However, when OA were split into high- and low-performance groups according to their task performance, the High-OA group showed a 'youth-like' load dependent BOLD response that could be indicative of brain maintenance. This result may seem contradictory to aforementioned studies focusing on reserve and functional compensation in OA compared to YA (Cabeza et al., 2002; Duarte et al., 2008; Meusel et al., 2017; Springer et al., 2005). However, it is arguable that all three concepts function together in healthy aging to support cognitive functions, i.e. episodic memory. For example, Hayes, Hayes, Williams, Liu, and Verfaellie (2017) examined associations between cardiorespiratory fitness (CRF) and fMRI activity in OA and YA during an associative encoding task in which participants were asked to learn face-name associations. Results showed that in OA, CRF was positively correlated with task-related fMRI activity in several regions, including bilateral PFC, bilateral thalamus and left hippocampus. When OA were split into high- and low CRF performers relative to their younger counterparts, High-OA, but not Low-OA, showed similarities in fMRI activations to YA in several regions including thalamus and PFC. This pattern was interpreted as evidence for brain maintenance in the High-OA group. Interestingly, in other PFC regions, High-OA, but not Low-OA showed greater activation than YA. The pattern of over-activation seen in High-OA was also positively correlated with source memory performance and was taken as evidence for functional compensation. Therefore, age-related increases in brain activity that are coupled with better cognitive performance could be interpreted as compensatory, while similarity in brain activity patterns associated with better performance in both YA and OA could be taken as evidence for

brain maintenance. Proper deployment of compensatory responses in the aging brain may rely on the accumulation of neural resources mediated by reserve (Cabeza et al., 2018).

Therefore, increased variability in memory performance with advanced age may be related to individual differences in brain maintenance, reserve and/or compensation. To date the majority of fMRI studies of successful aging and memory have examined the influence of maintenance, reserve and compensation separately, made between group comparisons, and focused on one memory task and/or memory phase (i.e. encoding or retrieval). In the current study, we compare and contrast predictions based on the concepts of maintenance, compensation and reserve using task fMRI data from a large cohort adult lifespan study scanned during encoding and retrieval phases of two episodic memory tasks: left/right face-location spatial context memory tasks and least/most recent face temporal context memory task. In addition, each task was tested at two levels of task difficulty to explore the impact of task demands on memory performance and brain activity. Initial analyses of a subset of this dataset have been previously published (Ankudowich et al., 2016, 2017). In the current study we tested an additional 26 participants in this protocol (N = 154) and used multivariate behaviour partial least squares (B-PLS) analysis to examine how age, retrieval accuracy, and a proxy composite measure of reserve (consisting of years of education, and items from our neuropsychological test battery reflecting estimated premorbid intelligence, verbal memory ability, and executive function), similarly and differentially correlated with brain activity during spatial and temporal context encoding and retrieval. The continuous variables of reserve and retrieval accuracy were orthogonalized to the age variable to derive effects related to the accuracy and reserve terms, independent of age. B-PLS is a data-driven method that identifies whole-brain patterns of activation that maximally relate the experimental design and behavioural covariates of interest;

in this case – age, retrieval accuracy and reserve. Based on current definitions of brain maintenance, reserve and compensation, we predicted that if brain maintenance uniquely, and independently, contributed to sustained levels of retrieval accuracy with age, then we would identify significant patterns of brain activity that were uniquely correlated to retrieval accuracy, independent of age and reserve. In contrast, if compensation supported better memory performance with advanced age, we would identify a significant pattern of brain activity that were similarly correlated with increased age and improved memory performance, but not be strongly related to reserve. Finally, we predicted that if reserve contributed to better memory performance with advanced age, we would identify a pattern of whole brain activity that either similarly correlated with age, retrieval accuracy and our proxy measure of reserve; or similarly correlated with age and our proxy measure of reserve. The former finding would imply that greater reserve is associated with more compensation; the latter would imply that reserve alters brain activity with age, which may not be directly related to task-specific performance.

2. Methods

2.1 Participants

One hundred and fifty-four healthy adults (age range 19-76 yrs, mean age = 48.08 yrs; 109 females; mean years of formal education [EDU] = 15.66 yrs) participated in this study. Of the 154 participants tested, 42 were young (age range 19-35 yrs, mean age = 25.81 yrs; 28 females; EDU = 16.21 yrs), 68 were middle-aged (age range 40-58 yrs, mean age = 50.00 yrs; 51 females; EDU = 15.35 yrs), and 44 were old (age range 60-76 yrs, mean age = 66.39 yrs; 30 females; EDU = 15.61 yrs). The age groups did not differ in level of education. All participants were right-handed as assessed by the Edinburgh Inventory for Handedness (Oldfield, 1971), had no history of neurological or psychological illness, and had no family history of Alzheimer's

disease.

Participation involved two sessions conducted on two separate days. During the first session, participants completed a battery of neuropsychological measures assessing their eligibility. The measures consisted of the Folstein Mini Mental State Examination (MMSE), exclusion cut-off < 27, (Folstein, Folstein, & McHugh, 1975); the Beck Depression Inventory (BDI), exclusion cut-off < 15, (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the American National Adult Reading Test (NART) used as a proxy for premorbid intelligence, inclusion cut-off ≤ 2.5 SD, (Nelson & Wilison, 1991), and a practice run of the context memory tasks in a mock MRI scanner. The California Verbal Learning Test (CVLT) Delay Free Recall (DFR), CVLT Delay Cued Recall (DCR), and CVLT Delay Recognition (DRG) was also administered to assess long term memory recall (Delis, Kramer, Kaplan, & Thompkins, 1987). To assess executive function, WCST (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) and the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) verbal fluency test; Letter Fluency (LF), Category Fluency (CF), and Category Switching (CS), were also administered. Additional medical exclusion criteria included: having a history of diabetes, untreated cataracts and glaucoma, smoking > 40 cigarettes a day, and a current diagnosis of high cholesterol and/or high blood pressure that has been left untreated in the past six months. Individuals who met the neuropsychological inclusion criteria and performed above chance on the mock-MRI scanner trials, were invited to participate in a second fMRI testing session. All participants were paid and provided their informed consent to participate in the study. The ethics board of the Faculty of Medicine at McGill University approved the study protocol.

2.2 Behavioural methods

Details concerning the methods and stimuli pertaining to the fMRI task have previously been outlined in Kwon et al. (2016). In brief, a mixed rapid event-related fMRI design was implemented in which participants were scanned while encoding and retrieving the spatial context (whether a face had appeared on the left or the right side of the screen during encoding) or temporal context (whether a face had appeared most or least recently at encoding) of face stimuli. Participants completed 12 experimental runs of easy and difficult versions of the spatial and temporal tasks. Each run consisted of one spatial easy (SE) and one temporal easy (TE) context memory task, in addition to either a spatial hard (SH), or temporal hard (TH) task. During easy tasks, participants encoded 6 face stimuli and during hard tasks participants encoded 12 face stimuli.

The task stimuli set has been used in previous studies (Rajah, Ames, & D'Esposito, 2008; Rajah et al., 2010), and consisted of black and white faces of different ages. All face stimuli were cropped at the neck and were rated for pleasantness by two independent raters. The age and sex of the faces were balanced across experimental conditions and were each presented only once at encoding without replacement. Faces shown at encoding were subsequently tested at retrieval.

2.2.1 Encoding phase

At the start of each encoding phase, participants were cued (9s) to memorize either the spatial location or temporal order of the ensuing faces, then either six (i.e., easy) or 12 (i.e., hard) faces were serially presented to the left or right side of a centrally presented fixation cross. Each stimulus was presented for 2s followed by a variable ITI (2.2-8.8s). Participants were also asked to rate the pleasantness of each face as pleasant or neutral during encoding. This was done to ensure subjects on task and encoded the faces. In total, participants performed 12 SE, 12 TE, 6 SH, and 6 TH tasks, yielding a total of 72 encoding events per task-type (i.e., 288 total encoding

events). Following the encoding phase of each run, participants performed an alphabetization distraction task (60s) where they were asked to select the word that comes first in the alphabet. The distraction task served to minimize working-memory related rehearsal of encoded information.

2.2.2 Retrieval phase

After the distraction task, participants were cued (9s) that the retrieval phase (spatial or temporal) was about to begin. Depending on the retrieval task cued, participants were presented with two previously encoded faces above and below a central fixation cross and were either asked which face was originally presented to the left (or right) side of the screen during encoding (spatial context retrieval), or was originally seen least/most recently (temporal context retrieval). Easy retrieval tasks consisted of three retrieval pairs and hard retrieval tasks consisted of six retrieval pairs, for a total of 36 retrieval events per task type. Each retrieval pair was presented for 6s followed by a variable ITI (2.2-8.8s).

2.3 Behavioural data analysis

Repeated-measures mixed effects ANOVAs were conducted on retrieval accuracy (% correct) and reaction time (msec) with group (3: young, middle-aged, older adults) as a between-subjects factor, and task (2: spatial, temporal) and difficulty (2: easy, hard) as within-subject factors, to determine significant group, task and difficulty main effects, and interactions (significance threshold $p < 0.05$). Post-hoc tests were conducted as needed to clarify significant effects and interactions.

2.4 MRI methods

Structural and functional MRI scans were collected on a 3T Siemens Trio scanner at the Douglas Institute Brain Imaging Centre. Participants wore a standard 12-channel head coil while

lying in supine position. T1-weighted anatomical images were acquired at the beginning of the fMRI testing session using a 3D gradient echo MPRAGE sequence (TR = 2300 ms, TE = 2.98 ms, flip angle = 9°, 176 1 mm sagittal slices, 1 x 1 x 1 mm voxels, FOV = 256 mm^2). FMRI BOLD images were acquired using a single shot T2*-weighted gradient echo planar imaging (EPI) pulse sequence (TR = 2000 ms, TE = 30 ms, FOV = 256 mm^2, matrix size = 64 x 64, in plane resolution 4 x 4 mm, 32 oblique 4 mm slices with no slice gap) during the context memory task. Jitter was added to the event-related acquisitions by means of a mixed rapid event related design with variable ITI (as stated above).

Visual task stimuli were back projected onto a screen in the scanner bore and was made visible to participants lying in the scanner via a mirror mounted within the standard head coil. The stimuli were generated on a computer using E-Prime (Psychology Software Tools, Inc.; Pittsburgh, PA, USA) software. Participants requiring visual acuity correction wore corrective plastic lenses and a fiber optic 4-button response box was supplied to participants to make responses during the task.

2.4.1 Pre-processing

Images were converted from DICOM to ANALYZE format using Statistical Parametric Mapping (SPM) version 8 software (http://www.fil.ion.ucl.ac.uk/spm) run with MATLAB (www.mathworks.com). SPM8 was used for pre-processing on a Linux platform. To ensure that all tissue had reached steady state magnetization, images acquired during the first 10s were discarded from analysis. The origin of functional images for each participant was reoriented to the anterior commissure of the T1-weighted structural image. Functional images were then realigned to the first BOLD image and corrected for movement using a 6 parameter rigid body spatial transform and a least squares approach. Participants with > 4 mm movement were

excluded from further analysis. Functional images were then spatially normalized to the MNI EPI template (available in SPM) at 4 x 4 x 4 mm voxel resolution, and smoothed with an 8 mm full-width half maximum (FWHM) isotropic Gaussian kernel. ArtRepair toolbox for SPM8 was used to correct for bad slices prior to realignment and for volume artificats after normalization and smoothing (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-softwarte.html).

2.4.2 Multivariate PLS analysis

Multivariate Behavioural PLS (B-PLS) was used to identify whole brain patterns of task-related activity that correlate with age, reserve, and/or task accuracy during encoding and retrieval. This method was selected due to its ability to identify spatially and temporally distributed voxel activation patterns that are differentially related to the experimental conditions and/or correlated with the behavioural vectors of choice (McIntosh, Chau, & Protzner, 2004). The first step in the B-PLS analysis was to represent the fMRI data for correctly encoded and retrieved events in an fMRI data matrix. To do this, the three-dimensional event-related fMRI data were converted to a two-dimensional data matrix by 'flattening' the temporal dimension (t), so that time series of each voxel (m) is stacked side-by-side across the columns of the data matrix (column dimension = m*t). The rows of the 2D data matrix for an individual subject represented the event-related activity for all events for a given experimental condition i.e. SE encoding, SH encoding, TE encoding, TH encoding, SE retrieval, SH retrieval, TE retrieval, TH retrieval (row dimension = events*conditions). The event-related data for each event-type was averaged within subject, and subjects' fMRI data were stacked. The stacked data matrix contained the fMRI data for each event onset (time lag =0) as well as the subsequent seven TRs/time lags (TR = 2 sec * 7 = 14 sec) following event onset for *successfully* encoded and *successfully* retrieved events. .

The fMRI data matrix was then cross-correlated with three vectors, stacked in the same subject order: age, reserve-residual, and task accuracy-residual. We describe the calculation of the reserve and task accuracy residuals below. The resulting cross-correlation matrix was then submitted to singular value decomposition (SVD), which yielded mutually orthogonal latent variables (LVs). Each LV consists of: i) a singular value, reflecting the amount of covariance explained by the LV; ii) a correlation profile, which reflects how age, reserve-residual, and/or retrieval accuracy-residual vectors correlate with a pattern of whole-brain activity identified in the singular image (described next); iii) a singular image, which depicts a pattern of brain saliences, reflecting numerical weights assigned to each voxel at each TR/time lag included in the data matrix. These brain saliences represent a pattern of whole-brain activity that is symmetrically related to the correlation profiles for the 3 behavioural vectors. Brain regions with positive saliences are positively related to the correlation profile (with 95% confidence intervals), while those with negative saliences are negatively related to the correlation profile (with 95% confidence intervals). Since each LV reflects a symmetrical pairing of correlation profiles with a pattern of whole-brain activity, the inverse can also be implied; positive values in the correlation profile indicate a negative correlation with negative salience brain regions, and negative values indicate a positive correlation with negative salience brain regions.

Significance of LVs was assessed through 1000 permutations. The permutation test involved sampling without replacement to reassign link between subjects' behavioural vector measures and event/condition within subject. For each permuted iteration a PLS was recalculated, and the probability that the permuted singular values exceeded the observed singular value for the original LV was used to assess significance at

$p<0.05$(McIntosh et al., 2004). To identify stable voxels that consistently contributed to the correlation profile within each LV, the standard errors of the voxel saliences for each LV were estimated via 500 bootstraps, sampling subjects with replacement while maintaining the order of event types for all subjects. For each voxel, a value similar to a z-score known as the bootstrap ratio (BSR) was computed, reflecting the ratio of the original voxel salience to the estimated standard error for that voxel. Voxels with BSR values of ± 3.28 (equivalent to $p < 0.001$) and a minimum spatial extent = 10 contiguous voxels, were retained and highlighted in the singular image. BSR values reflect the stability of voxel saliences. A voxel salience whose value is dependent on the observations in the sample is less precise than one that remains stable regardless of the samples chosen (McIntosh & Lobaugh, 2004).

To determine at which time lags the correlation profile in a given LV was strongest, we also computed temporal brain scores for each significant LV. Temporal brain scores reflect how strongly each participant identifies with the pattern of brain activity expressed in the singular image in relation to its paired correlation profile, at each time lag. Peak coordinates are only reported from time lags at which the correlation profile was maximal differentiated within the temporal window sampled (lags 2-5; 4-10s after event onset). These peak coordinates were converted to Talairach space using the icbm2tal transform (Lancaster et al., 2007) as implemented in GingerAle 2.3 (Eickhoff et al., 2009). Since our acquisition incompletely acquired the cerebellum, peak coordinates from this region are not reported. The Talairach and Tournoux atlas (Talairach & Tournoux, 1998) was used to identify the Brodmann area (BA) localizations of significant activations.

Calculation of reserve and task accuracy vectors

The proxy measure for reserve used neuropsychological test data and EDU. Every participant's raw score on the CVLT-DFR, DCR, DRG; D-KEFS-LF, CF, CS; WCST categories completed, and correct responses (%); estimated IQ using NART scores; and EDU were standardized by z-score transformation based on the full sample. An average standardized score was then computed for every participant based on the z-scores of the 10 items mentioned above to yield a composite reserve score. These items were selected because we were interested in creating an overall reserve measure that provides a proxy of memory ability (CVLT; Delis et al., 1987), executive function (D-KEFS, and WCST; Delis et al., 2001; Heaton et al., 1993), and cognitive reserve (IQ, and EDU; Tucker & Stern, 2011). Once this composite measure was created, we conducted a regression analysis in which age (X) was used to predict reserve (Y) to obtain the reserve-residual (error) vector that would be uncorrelated to the age-vector. Similarly, we ran another regression analysis in which age (X) was used to predict task-specific retrieval accuracy (Y) to obtain the task accuracy-residual (error) vector that would be uncorrelated to the age-vector.

3. Results

3.1 Behavioural results

Table 1 summarizes demographics, neuropsychological test data, and context memory performance for all groups. One-way ANOVAs indicated there was a significant age-group difference on the composite reserve measure ($F[2,151] = 10.84$, $p < 0.001$, $\eta2 = 0.126$) due to the fact that younger and older adults scored higher than middle-aged adults. Additionally, younger adults outperformed middle-aged adults on the CVLT delay free recall ($F[2,151] = 3.94$, $p = 0.021$, $\eta2 = 0.050$), and completed more categories on the WCST ($F[2,151] = 13.73$, $p < 0.001$, $\eta2$

= 0.154) than both middle-aged and older adults. Younger adults were also more accurate on the WCST ($F[2,151] = 12.96$, $p < 0.001$, $\eta 2 = 0.146$) than both middle-aged and older adults. On the D-KEFS category fluency, older adults outperformed both younger and middle-aged adults ($F[2,151] = 7.79$, $p < 0.001$, $\eta 2 = 0.094$).

3.1.1 Accuracy results

The group (3) x task (2) x difficulty (2) repeated-measures (RM) ANOVA on retrieval accuracy revealed a significant main effect of group ($F[2, 151] = 22.19$, $p < 0.001$, $\eta 2 = 0.227$), task ($F [1, 151] = 763.30$, $p < 0.001$, $\eta 2 = 0.835$), difficulty ($F [1, 58] = 115.33$, $p < 0.001$, $\eta 2 = 0.433$), and a task x difficulty interaction ($F [1, 151] = 34.76$, $p < 0.001$, $\eta 2 = 0.187$). Tukey's HSD post-hoc test indicated that the significant main effect of group was due to younger adults outperforming both middle-aged and older adults, and middle aged adults outperforming older adults across conditions (ps < 0.001). Across groups, participants performed better on the spatial compared to the temporal task, and on easy vs. hard tasks. However, the significant task x difficulty interaction indicated that the difficulty manipulation impacted accuracy scores more on the temporal task ($t(1,153) = 11.22$, $p < 0.001$), compared to the spatial task ($t(1,153) = 4.82$, $p < 0.001$).

3.1.2 Reaction time results

The group (3) x task (2) x difficulty (2) RM ANOVA on retrieval reaction time (RT) revealed a significant main effect of group ($F[2, 151] = 12.93$, $p < 0.001$, $\eta 2 = 0.146$), task ($F [1, 151] = 204.04$, $p < 0.05$, $\eta 2 = 0.575$), and difficulty ($F [1, 58] = 31.19$, $p < 0.05$, $\eta 2 = 0.171$). Tukey's HSD post-hoc test indicated that younger adults responded faster than both middle-aged and older adults across conditions (ps < 0.001). Across groups, participants were slower on the temporal compared to the spatial task, and on hard vs. easy tasks (ps < 0.001).

3.2 fMRI results

The B-PLS analysis revealed four significant LVs linking whole-brain patterns of activity to the behavioural vectors of age, reserve (residulaized), and task accuracy (residualized). LV1 accounted for 20% of the total cross-block covariance ($p < 0.001$). Only negative salience brain regions from this LV survived our spatial threshold cut-off of 10 contiguous voxels ($p < 0.001$), and the local maxima of those negative saliences are presented in Table 2. Figure 1a shows the PLS correlation profile separated by task (SE, SH, TE, and TH), and the corresponding singular image presented in Figure 1b demarcates the stable negative salience regions (cool coloured regions). The PLS correlation profile indicates that this LV was mostly related to easy events across both tasks (spatial and temporal). Specifically, activity in negative salience brain regions increased with age during easy encoding events (SE, and TE). Activity in those regions also increased with reserve, and was correlated positively with subsequent accuracy for the same easy spatial and temporal encoding events. Interestingly, activity in negative salience regions was also positively correlated with accuracy at easy spatial and temporal retrieval events. In other words, LV1 primarily identified negative salience brain regions in which event-related activity increased with age, reserve, and accuracy during easy events at encoding, and increased with retrieval accuracy during easy events. These regions included: bilateral fusiform gyrus (BA 18), ventrolateral PFC (BA 44), inferior parietal lobule (IPL: BA 40), frontal eye-fields (FEF: BA 8), left anterior temporal cortex (BA20/21), left hippocampus, and other regions (see Table 2).

LV2 accounted for 12.17% of the total cross-block covariance ($p < 0.001$), and primarily reflected a main effect of age identifying a whole-brain pattern of linear increases of activity with age across all encoding and retrieval events. The PLS correlation profile and the corresponding singular image are presented in Figures 2a and 2b respectively. Local maxima

denoting positive and negative saliences for this LV are presented in Table 3. Age was positively correlated with activity in bilateral IPL, temporal cortex and right PHG (BA 36); and negatively correlated with activity in left fusiform cortex, posterior cingulate and thalamus. Interestingly, at age-related increases in right PHG and bilateral IPL activity at encoding was negatively correlated with reserve (except for SE task), but age-related increases in activity at retrieval in these same regions was negatively correlated with accuracy for temporal context tasks. However, overall while some of the effects observed in this LV may be attributed to reserve or accuracy, this LV is fairly identical to LV1 in our previous study (Ankudowich et al., 2016) and most strongly represent the effect of age on encoding and retrieval related activity across all tasks.

LV3 accounted for 10.18% of the total cross-block covariance ($p < 0.001$) and mainly identified brain regions that were differentially related to age during encoding and retrieval (age x phase effect). The local maxima of positive and negative voxel saliences from this LV are presented in Table 4. The PLS correlation profile for this LV is presented in Figure 3a, and the corresponding singular image is presented in Figure 3b. Based on the PLS correlation profile for LV3, activity in positive salience brain regions (warm coloured regions in Figure 3b) was positively correlated with age during retrieval conditions (except TH retrieval), and negatively correlated with age at encoding. Moreover, activity in those regions at retrieval was also positively correlated with reserve during spatial context memory tasks (SE and SH retrieval). Positive salience brain regions included: bilateral hippocampus, IPL (BA 40), right lingual gyrus (BA 19), caudate, and ventrolateral PFC (BA 44). In contrast, activity in negative salience regions (blue coloured regions in Figure 3b) was positively correlated with age across all encoding conditions, and negatively correlated with age and with reserve (for spatial context

tasks) during retrieval. Negative salience brain regions included: bilateral fusiform gyrus (BA 18/19), left postcentral gyrus (BA1/2), precuneus (BA 7), and right anterior PFC (BA 10).

LV4 accounted for 6.30% of the total cross-block covariance ($p < 0.001$) and identified a pattern of brain activity that was mainly related to reserve, independent of age. Only negative salience brain regions from this LV survived our spatial threshold cut-off of 10 contiguous voxels ($p < 0.001$), and the local maxima of those regions are presented in Table 5. Based on the PLS correlation profile (Figure 4a) and the corresponding singular image (Figure 4b), activity in left middle frontal gyrus (BA 6), left fusiform gyrus (BA 37), right precentral gyrus (BA 4), caudate, and FEF (BA 8), was negativity correlated with reserve during all retrieval conditions (and encoding SE). Activity in those regions also increased with age during easy retrieval tasks (SE and TE retrieval).

4. Discussion

In the current study, we were interested in testing predictions related to the role of brain maintenance, reserve and compensation on supporting/maintaining episodic memory for spatial and temporal contextual details across the adult lifespan. We created a composite measure of reserve using levels of educational attainment, premorbid intelligence, and items from a neuropsychological test battery reflecting verbal memory ability and executive function. We then submitted this continuous vector of reserve, along with the vectors of age and retrieval accuracy to B-PLS analysis in order to examine how the 3 behavioural vectors interact and modulate patterns of activity across the whole brain during easy and hard, spatial and temporal context memory encoding and retrieval phases. The behavioural results showed the typical pattern of age-related decrements in context memory retrieval accuracy across all tasks. As expected, YA outperformed middle-aged and OA, and middle-aged adults performed better than OA. This is

consistent with prior findings suggesting that context memory declines begin as early as mid-life (Cansino, 2009), and persist into older adulthood (Simons, Dodson, Bell, & Schacter, 2004; Wegesin, Jacobs, Zubin, Ventura, & Stern, 2000). Participants in the current study also showed higher accuracy on easy relative to hard tasks, implying that increasing encoding load increased task difficulty.

To explore how interindividual differences in reserve impacted task performance, we ran within-age group, and across-age group correlations between the composite reserve measure and retrieval accuracy for each task (i.e., SE, SH, TE, and TH). Within-age group correlations failed to reach significance threshold for any of the tasks per age group. Yet, reserve was positively correlated with spatial hard ($r(154) = 0.20$, $p = 0.013$), and temporal hard ($r(154) = 0.25$, $p = 0.002$) retrieval accuracy across participants. Therefore, at higher levels of task difficulty, participants with higher levels of reserve showed better context memory performance. These results converge with previous findings showing that reserve may mitigate episodic memory decrements across a wide age range in healthy individuals (Corral, Rodriguez, Amenedo, Sanchez, & Diaz, 2006), through enhanced ability of coping with additional task demands (Stern, 2002).

In relation to the fMRI findings, our B-PLS analysis revealed four significant orthogonal LVs showing whole brain activity patterns that correlated with age, reserve, and/or task accuracy. LV1 revealed that during easy encoding events, age-related increases in several regions including inferior parietal, PFC, and ventral visual processing areas, were associated with individual differences in reserve and predicted better subsequent memory. Consistent with our predictions for the reserve and compensation models, this LV demonstrated that task-specific compensatory responses in the aging brain are modulated by individual differences in reserve.

LVs2 and 3 both showed patterns of brain activity that were most strongly related to age, but were also associated with reserve. Although many of the regions revealed in those LVs overlap with those in LV1, the age-related patterns shown in LV2 and LV3 were not consistently associated with better memory performance and hence cannot be considered compensatory. Nevertheless, these patterns demonstrate that some of the more global age-related effects observed during encoding and retrieval are also related to individual differences in reserve. The last LV explained the least amount of covariance in the B-PLS analysis. This fourth LV mainly revealed a pattern of activity that increased with age during easy retrieval events, but decreased with reserve across all retrieval conditions, consistent with the notion that individuals with higher reserve may exhibit enhanced neural efficiency (Stern, 2009). Below, we discuss these findings and their implications in further detail.

Age-related compensatory activity patterns modulated by reserve (LV1)

LV1 explained the largest amount of covariance in our B-PLS analysis and identified a set of distributed negative salience brain regions including bilateral occipital-temporal cortices, IPL, precuneus and PFC. Activity in these regions increased with age and reserve during easy context encoding tasks and was positively correlated with subsequent memory on these tasks. These results are consistent with the hypothesis that greater reserve may relate to more compensatory activation in older age. During retrieval, activity in those regions also appeared to support performance on easier versions of the task, albeit not in association with age or reserve. This implies that at retrieval, re-activation of the same network of regions initially recruited during encoding supports memory accuracy for the same event types, adding to the rich body of literature arguing that successful recollection hinges on reinstatement or recapitulation of the cognitive and/or neural processes engaged during memory encoding (Buckner & Wheeler, 2001;

Rugg, Johnson, Park, & Uncapher, 2008; Tulving, Voi, Routh, & Loftus, 1983; Waldhauser, Braun, & Hanslmayr, 2016; Wheeler, Petersen, & Buckner, 2000).

As stated above, the effects in LV1 were reliably observed in ventral occipital cortex (BA18/37) and lateral inferior and middle temporal cortices (BA 20, 21). We have previously shown that age was positively associated with ventral occipital and fusiform cortex at encoding, but this was not correlated to subsequent memory (Ankudowich et al., 2017). Instead, ventral occipital and fusiform activity at retrieval was positively correlated with memory performance; however, older adults exhibited reduced activity in these ventral occipital cortex regions at retrieval. We also found that age was positively correlated with lateral temporal activity across context encoding and retrieval tasks, but this was not positively correlated with memory performance. Interestingly, LV1 in the current study revealed a novel finding that reserve was related to an age-related increase in both ventral occipital and lateral temporal activation during easy encoding tasks, and this was related to better subsequent memory. These ventral occipital cortical regions, including fusiform cortex, have consistently been shown to be related to face processing and recognition (Haxby, Hoffman, & Gobbini, 2000; Loffler, Yourganov, Wilkinson, & Wilson, 2005; Rotshtein, Henson, Treves, Driver, & Dolan, 2005). In contrast, previous neuroimaging studies of memory have shown that activity in lateral temporal regions support more generalized semantic/conceptual processing of visual stimuli (Binder & Desai, 2011; Menon, Boyett-Anderson, Schatzberg, & Reiss, 2002). Therefore, our current results suggest that individuals with higher reserve may be better positioned to engage a variety of visual encoding strategies with advanced age, and that this benefits successful memory encoding and retrieval.

Individuals with more reserve also activated left anterior hippocampus more with advanced age at encoding. The anterior hippocampus has been shown to be more active during

episodic encoding, compared to retrieval (Kim, 2015; Lepage, Habib, & Tulving, 1998) and to contribute to relational processes (Davachi et al., 2006) and conceptual encoding requiring the integration of a variety of perceptual, emotional and semantic information (Zeidman & Maguire, 2016). We have previously shown that larger anterior hippocampal volumes were associated with better spatial and temporal context memory in young adults (Rajah et al., 2010). We also found that age-related reduction in anterior hippocampal volumes was associated with increased encoding activity in occipital, lateral temporal and PFC, which was also associated with better subsequent memory for easier, compared to harder, context memory task in older adults (Maillet & Rajah, 2013). The current results dovetail nicely with our prior findings and indicate that older adults with higher reserve were better able to co-activate anterior hippocampal, occipital-temporal and PFC regions (discussed below) at encoding, which benefitted subsequent memory during easy tasks.

LV 1 also identified activations in precuneus and inferior parietal regions (BA 7 and BA 40 respectively), ventrolateral PFC (BA 44) and dorsal PFC (BA8; frontal eye fields). Evidence from the attention literature points to the presence of two functionally distinct attention systems in the human brain . A dorsal fronto-parietal system involving superior parietal (precuneus) regions and frontal eye-fields, which is thought to be involved in top-down allocation of attentional resources to locations or different features; and a ventral fronto-parietal system involving inferior parietal regions and ventrolateral PFC, which is thought to be involved in stimulus-driven, bottom-up shifts in attentional focus. Whether age- and reserve-related increases in fronto-parietal activity observed in LV1 reflected supervisory top-down, or stimulus-driven bottom up attentional processes cannot be discerned from the current results. Nevertheless, recent evidence suggests that these two systems do not operate independently and interact to

allow for the flexible control of attention in response to current task demands (Vossel, Geng, & Fink, 2014). Our current results indicate that older adults with greater reserve may be better able to recruit frontoparietal cognitive control processes to modulate the engagement of the aforementioned visual and mnemonic strategies to benefit memory performance during easy context memory tasks.

Importantly, while the pattern of results in LV1 identified brain regions that supported task performance with advanced age, age-related deficits were still apparent. It is hypothesized that neural resources thought to counteract the effects of age-related decline accumulate as a function of reserve (Barulli & Stern, 2013; Stern, 2002, 2009). Although accumulated neural resources may completely offset age-related deficits, they attenuate those declines in a more typical scenario (Cabeza et al., 2018). In the current study, since the pattern of age-related over-recruitment observed in LV1 was associated with better task performance, it can be regarded as a form of functional compensation (Cabeza & Dennis, 2013; Grady, 2008; Rajah & D'Esposito, 2005) to cope with task demands even at easier versions of the context memory task. At higher levels of task difficulty (i.e., SH and TH), the set of brain regions that aided performance on easy tasks were no longer associated with age, reserve, or performance.

It is conceivable that easier versions of the task in the current study placed higher cognitive demands as a function of age, and older individuals with higher levels of reserve were better able to engage occipito-temporal, hippocampal and frontoparietal brain regions to support task performance. This interpreation is consistent with the CRUNCH model (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Lustig, 2005), which suggests that load-sensitive, task-related brain regions are recruited in older age at lower levels of task demands compared to YA who may recruit those regions at higher levels of task demand. The fact that age-related decrements in

accuracy were observed in both spatial easy ($F(2,151) = 6.88$, $p < 0.001$, $\eta^2 = 0.083$), and temporal easy ($F(2,151) = 11.87$, $p < 0.001$, $\eta^2 = 0.136$) tasks lends further support to this interpretation. Therefore, findings from LV1 suggest that demand-related compensatory responses observed with increased age during memory encoding are modulated by individual differences in reserve.

Non-compensatory activity patterns reflecting an age x reserve interaction (LVs 2, 3, & 4)

The B-PLS analysis in the current study revealed two additional LVs representing patterns of event-related activity that were most strongly attributed to age, but were also modulated by reserve. Specifically, LV2 revealed a linear trend of age-related increases and decreases in brain activity across all task conditions. Since age is related to changes in cerebrovascular and metabolic processes that contribute to the blood-oxygen-level-dependent (BOLD) response measured by fMRI, it is possible that the general pattern of age-related differences in activity identified by LV2 may reflect non-cognitive factors (Gazzaley & D'Esposito, 2004). However, this pattern of brain activity was also associated with reserve during memory encoding (except for SE encoding), and some of the regions identified in this LV overlap with activations observed in LV1; thus, suggesting that LV2 may not reflect effects associated with age-related differences in cerebrovascular and metabolic function. Overall, LV2 indicated that age was related to increases in ventral occipital, lateral temporal, right parahippocampal and inferior parietal activity, and decreases in fusiform cortex activity across encoding and retrieval for all tasks

LV3 revealed a more refined pattern of activity that was differentially related to age at encoding and retrieval, and to reserve during spatial context memory retrieval. Specifically, LV3 indicated that activity in lingual, bilateral posterior hippocampal and bilateral inferior parietal

cortical activity increased with age at retrieval and with reserve during spatial context retrieval; but activity in bilateral fusiform and anterior PFC decreased with age at retrieval. Importantly, these age-related differences in retrieval activity were greater in older adults with higher reserve. In contrast, during encoding the opposite pattern of activity was observed with advanced age.

Overall, findings from LV2 and LV3 are largely consistent with observations from previous fMRI studies of episodic memory across the adult lifespan and with results from LV1 and show that in general, aging may be related to increases in lateral occipital-temporal, medial temporal and parietal regions activity, and decreases in fusiform activity (e.g., Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Kennedy et al., 2012). By considering the first three LVs together, we observe that some of the age-related increases may be more apparent at encoding (lateral occipital-temporal, PFC), and others at retrieval (medial temporal, parietal). In addition, age-related decreases in fusiform and PFC may be more apparent at retrieval. Importantly, however, our current study suggests the majority of these age-related differences in activity are modulated by individual differences in reserve. For example, LV2 shows that higher reserve was associated with increased activity in the lateral occipital cortex during memory encoding, which suggests that age-related attenuations in visual cortical processing may be minimized in individuals with higher levels of reserve, consistent with the notion that reserve may mitigate age-related decline in brain function (Cabeza et al., 2018; Tucker & Stern, 2011). Moreover, the overlap between activations in LV2, LV3 and LV1 indicates that some of these age- and reserve-related differences in brain activity benefitted memory functions.

Our last significant LV (LV4) identified a small subset of brain regions, including left fusiform and motor cortices, which showed reserve-related decreases in activity during retrieval and age-related increases in activity during easy context retrieval tasks. In addition to

compensation, higher reserve has also been hypothesized to relate to higher neural efficiency as indexed by lower activity in task-related brain regions (Barulli & Stern, 2013; Steffener & Stern, 2012; Stern, 2009). One speculative interpretation is that individuals with high reserve may have more efficient visuomotor processing at retrieval; and that this efficient processing declines with age. There is some evidence for enhanced neural efficiency in healthy younger and OA such as those with higher reserve exhibit reduced task-related activation compared to those with lower levels of reserve (Habeck et al., 2003, 2005; Steffener, Reuben, Rakitin, & Stern, 2011). However, given that LV4 only accounted for 6.30% of the total cross-block covariance, it remains unclear what the findings from this LV may reflect and whether they would generalize across studies.

The medial temporal lobes, reserve and compensation

Distinct regions of the medial temporal lobes were identified across LVs 1 through 3. Increased age-related activity in left anterior hippocampus was observed in LV1, and was positively correlated with reserve and subsequent memory. Age-related increases in right PHG was observed at encoding and retrieval, and age-related increases in bilateral posterior HC were observed at retrieval (LV3). Interestingly age-related increases in right PHG activity at encoding, was negatively related to reserve, but age-related increases in bilateral posterior hippocampus and anterior hippocampus activity were positively related to reserve. Together, these observations suggest that individuals with higher vs. lower reserve may exhibit age-related differences in hyperactivation within the MTL. Age-related increases in hippocampal activity may be positively related to reserve, and this suggests that older adults with higher vs. lower reserve may exhibit different patterns of MTL hyper activation during encoding vs. retrieval. There has been significant interest in the cognitive neuroscience of aging and dementia fields on

whether age-related increases in MTL activation reflect compensation in healthy aging (Cabeza et al., 2018), or whether these 'hyperactivations' may reflect a neurotoxic response in the aging brain which may be an early sign of pathological aging (Bookheimer et al., 2000; Fleisher et al., 2009; Quiroz et al., 2010). Our results suggest that individuals with high reserve exhibit increased hippocampal activity with age, and that this increase at encoding may reflect compensation. In contrast, it is less clear whether the increased parahippocampal activation in lower reserve adults in advanced age is detrimental to performance or not. This is an important topic for future research, given the importance of hippocampal function in memory and the rich literature implicating age-related difference in MTL function in both healthy and pathological aging.

Limitations and conclusion

In the current study, we failed to observe activity patterns supporting brain maintenance. Based on our predictions for the maintenance model, we expected to observe patterns of activity that were uniquely associated with retrieval accuracy, independent of age or reserve. This would suggest that preserved memory ability relies on minimal age-related brain changes (Nyberg et al., 2012). The absence of support for brain maintenance in the current study should not be regarded as evidence against the maintenance model. Brain maintenance postulates that memory performance is greatest in individuals who show minimal age-related changes when followed over time. This implies that a longitudinal approach would be best at testing this hypothesis. It is possible that our cross-sectional design failed to capture patterns of activity suggestive of maintenance and rather reflected cohort-differences between our age groups. Furthermore, cross-sectional studies lending support to the maintenance model typically compare and contrast activity patterns in High-OA, Low-OA and YA, and show similarities in activity patterns

between High-OA, and YA, but not Low-OA (e.g., Nagel et al., 2009). Therefore, our within-group B-PLS analysis with age as a continuous behavioural vector may have not been ideal in testing predictions related to brain maintenance. Future studies utilizing longitudinal approaches or cross-sectional studies examining between-group similarities and differences in high- and low-performance groups of YA and OA may be more suited for testing the brain maintenance model.

Conclusions

In sum, the current study provided novel evidence that reserve modulates task-specific compensatory brain responses as a function of task demands. In particular, encoding-related activity in fronto-parietal regions implicated in attention, in addition to occipito-temporal and anterior hippocampal activity increased with age, reserve and supported subsequent memory for easy context memory tasks. Additional patterns of activity exhibiting non-compensatory age by reserve interactions were also revealed in the current analysis, and included regions overlapping with those exhibiting a compensatory response such as areas of the lateral occipital-temporal cortex, medial temporal, and IPL regions. However, it is the co-activation of the aforementioned regions *along with the activation of PFC* that appeared to differentiate the whole-brain pattern of age- and reserve-related activations that reflected compensation. More notably, both compensatory and non-compensatory patterns related to age were modulated as a function of individual differences in reserve. This highlights the importance of considering reserve as a modulatory factor in future studies of brain and memory aging.

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Table 1. Demographics, neuropsychological test data, and context memory performance per age-group

	Young	Middle-aged	Old	p-value	η2
Sample size	42	68	44		
Age (Yrs)	25.81 (0.54)	50.00 (0.65)	66.39 (0.56)		
Gender (n, [%] females)	28 [67%]	51 [75%]	30 [68%]		
Reserve composite measure [a]	0.51 (0.11)	-0.29 (0.12)	0.13 (0.12)	< .001*	.126
EDU (Yrs)	16.21 (0.29)	15.35 (0.25)	15.61 (0.34)	.104	-
CVLT – DFR [b]	13.88 (0.27)	12.75 (0.26)	13.07 (0.33)	.021*	.050
CVLT – DCR	13.98 (0.27)	13.13 (0.24)	13.23 (0.30)	.072	-
CVLT – DRG	15.52 (0.10)	15.13 (0.13)	15.18 (0.13)	.084	-
WCST – categories completed [c]	8.52 (0.15)	6.51 (0.31)	6.32 (0.36)	< .001*	.154
WCST – % correct [c]	0.83 (0.07)	0.73 (0.15)	0.74 (0.17)	< .001*	.146
D-KEFS – LF	12.05 (0.46)	11.64 (0.43)	12.66 (0.52)	.302	-
D-KEFS – CF [d]	11.67 (0.50)	10.94 (0.43)	13.41 (0.41)	< .001*	.094
D-KEFS – CS	13.48 (0.47)	13.38 (0.38)	14.48 (0.36)	.131	-
Estimated IQ (NART)	119.62 (0.81)	118.00 (0.73)	120.35 (0.69)	.067	-
Accuracy (% correct)					
Spatial easy retrieval	0.89 (0.01)	0.86 (0.01)	0.82 (0.01)		
Temporal easy retrieval	0.77 (0.20)	0.70 (0.16)	0.65 (0.01)		
Spatial hard retrieval	0.89 (0.15)	0.81 (0.01)	0.77 (0.02)		
Temporal hard retrieval	0.68 (0.02)	0.59 (0.01)	0.54 (0.01)		
Reaction time (msec)					
Spatial easy retrieval	2198 (78.60)	2501 (63.12)	2781 (71.20)		
Temporal easy retrieval	2596 (84.51)	2966 (59.94)	3157 (88.97)		
Spatial hard retrieval	2303 (74.03)	2628 (54.12)	2837 (77.34)		
Temporal hard retrieval	2777 (95.58)	3099 (75.70)	3185 (93.30)		

Note: This table presents age-group means and standard errors between brackets for demographic, neuropsychological measures, and spatial and temporal context memory accuracy and reaction times. In addition, one-way ANOVA p-values and partial eta squared ($\eta 2$) values for demographic and neuropsychological measures are listed. EDU = Years of Education; CVLT = California Verbal Learning Test; DFR = Delay Free Recall; DCR = Delay Cued Recall; DRG = Delay Recognition; WCST = Wisconsin Card Sorting test; D-KEFS = Delis-Kaplan Executive Function System; LF = Letter Fluency; CF = Category Fluency; CS = Category switching; NART = American National Adult Reading Test.

Tukey's HSD post-hoc between-group tests were conducted at p = 0.05 to clarify group differences and are summarized as follows: [a] young & old adults > middle-aged adults; [b] young adults > middle-aged adults; [c] young adults > middle-aged & old adults; [d] old adults > young & middle-aged adults.

Table 2: Local maxima for LV1: regions where activity correlated with age, reserve, and task accuracy

Hemisphere	Temporal lag	Bootstrap ratio	Spatial extent	Talairach coordinates x	y	z	Gyral location	BA
Negative Saliences: Increased activity with age, reserve, and subsequent accuracy during easy encoding events, and increased activity that predicted task accuracy during easy retrieval events								
Left								
	3,5	-5.69	621	-23	-83	-15	Inferior Occipital/ Fusiform	18
	2,3	-5.52	1277	-64	8	24	Inferior frontal	44
	2,5	-5.32	3124	-39	-35	36	Inferior parietal lobule	40
	3	-5.14	207	-23	-14	-23	Hippocampus	-
	4	-5.00	2337	-5	-54	42	Precuneus	7
	3	-4.96	55	-19	2	1	Putamen	-
	4	-4.90	93	-31	-7	57	Middle frontal	4/6
	2,3,4	-4.84	71	-20	31	50	Superior frontal	8
	4,5	-4.72	28	-49	1	-25	Middle temporal	21
	2,4	-4.66	90	-38	-7	-15	Inferior temporal	20
	3	-4.35	79	-12	55	35	Superior frontal	9/10
	2,5	-4.14	54	-20	-64	23	Posterior cingulate	23/31
Right								
	2,3,5	-5.26	1292	50	-29	46	Inferior parietal lobule	40
	5	-5.25	49	25	-83	-10	Inferior Occipital/Fusiform	18
	2,3,4	-4.98	297	43	4	20	Inferior frontal	44
	2,4	-4.76	77	14	56	28	Superior frontal	9/10
	2	-4.64	281	2	-14	53	Medial frontal	6
	2	-4.62	43	17	-63	17	Posterior cingulate	31
	3	-4.3287	49	39	5	49	Middle frontal	6
	4	-4.2822	285	47	-54	-4	Middle/Inferior temporal	19
	4	-4.1524	72	28	25	36	Middle frontal	8
	4	-3.9827	50	40	-25	10	Superior temporal	41
	5	-3.9729	41	44	-19	-11	Middle temporal	21
	3	-3.7703	20	14	34	22	Anterior cingulate	32
	3	-3.64	11	44	33	-6	Inferior frontal	47

Note: Temporal lag refers to the time window (in secs) after event onset when a cluster of voxels exhibited an effect of interest. The bootstrap ratio identified dominant and stable activation clusters thresholded at ± 3.28. The spatial extent represents the total number of voxels in a voxel cluster (minimum = 10). The stereotaxic coordinates are measured in millimetres, and gyral location and Brodmann areas (BA) were determined through criteria outlined in Talairach and Tournoux (1998).

Table 3: Local maxima for LV2: Regions where activity correlated with age across encoding and retrieval phases

Hemisphere	Temporal lag	Bootstrap ratio	Spatial extent	Talairach coordinates x	y	z	Gyral location	BA
Positive Saliences: Increased activity with age across conditions, and decreased with reserve at encoding (except for spatial easy)								
Left								
	2,3	5.69	53	-57	-61	-6	Inferior temporal	37
	3	5.04	36	-61	-39	39	Inferior parietal	40
	4	4.77	35	-46	-79	-8	Inferior occipital	18/19
	4	4.58	31	-30	12	-24	Superior temporal	38
	3	4.04	33	-2	-18	57	Medial frontal	6
Right								
	4	6.45	756	25	-7	-25	Parahippocampal	36
	2,3	5.90	115	58	-40	45	Inferior parietal	40
	2	4.31	13	40	16	-26	Superior temporal	38
Negative Saliences: Decreased activity with age across conditions, and increased with reserve at encoding (except for spatial easy)								
Left								
	2	-5.72	103	-27	-75	-14	Fusiform/Lingual	18
	2	-3.71	11	-30	25	-1	Insula	13
Right								
	2	-5.83	211	-1	-26	23	Posterior cingulate	23
	5	-5.43	283	-1	-7	14	Thalamus	-

Note: Temporal lag refers to the time window (in secs) after event onset when a cluster of voxels exhibited an effect of interest. The bootstrap ratio identified dominant and stable activation clusters thresholded at ± 3.28. The spatial extent represents the total number of voxels in a voxel cluster (minimum = 10). The stereotaxic coordinates are measured in millimetres, and gyral location and Brodmann areas (BA) were determined through criteria outlined in Talairach and Tournoux (1998).

Table 4: Local maxima for LV3: regions where activity correlated with age differentially at encoding and retrieval

Hemisphere	Temporal lag	Bootstrap ratio	Spatial extent	Talairach coordinates x	y	z	Gyral location	BA
Positive Saliences: Increased activity with age at retrieval and decreased at encoding, and increased with reserve during spatial retrieval								
Left								
	5	4.95	165	-27	-43	7	Hippocampus	-
	3	4.16	20	-50	-42	28	IPL	40
	2	3.90	18	-23	7	-6	Putamen	-
Right								
	3	6.01	880	10	-54	-4	Lingual	19
	3,4	5.27	657	25	-41	19	Caudate	-
	5	5.07	198	14	-40	8	Hippocampus	-
	5	3.97	43	36	-46	29	IPL	40
	3	3.95	14	51	4	20	Inferior frontal	44
Negative Saliences: Increased activity with age at encoding and decreased at retrieval, decreased with reserve during spatial retrieval								
Left								
	2,3,5	-5.70	112	-39	-34	62	Postcentral	1/2
	2,3,5	-4.33	30	-13	-72	33	Precuneus	7
	5	-4.36	34	-34	-86	-19	Inferior Occipital	18
	5	-4.27	27	-57	-64	-10	Middle occipital/Fusiform	37
Right								
	3,4,5	-4.76	50	28	-85	4	Middle Occipital	18
	2	-4.35	16	29	57	17	Superior frontal	10
	5	-3.76	16	47	-19	-18	Inferior temporal	20

Note: Temporal lag refers to the time window (in secs) after event onset when a cluster of voxels exhibited an effect of interest. The bootstrap ratio identified dominant and stable activation clusters thresholded at ± 3.28. The spatial extent represents the total number of voxels in a voxel cluster (minimum = 10). The stereotaxic coordinates are measured in millimetres, and gyral location and Brodmann areas (BA) were determined through criteria outlined in Talairach and Tournoux (1998).

Table 5: Local maxima for LV4: regions that were predominantly related to age and reserve at retrieval

Hemisphere	Temporal lag	Bootstrap ratio	Spatial extent	Talairach coordinates x	y	z	Gyral location	BA
Negative Saliences: Regions were activity decreased with reserve at retrieval more generally and increased with age at easy retrieval								
Left								
	3	-4.63	29	-31	12	55	Middle frontal	6
	2	-4.31	29	-49	-57	-9	Fusiform	37
Right								
	3,4	-5.15	27	28	-19	68	Precentral gyrus	4
	2,3	-4.37	15	-1	13	9	Caudate	-
	3,4	-4.14	26	24	27	51	Superior frontal	8

Note: Temporal lag refers to the time window (in secs) after event onset when a cluster of voxels exhibited an effect of interest. The bootstrap ratio identified dominant and stable activation clusters thresholded at ± 3.28. The spatial extent represents the total number of voxels in a voxel cluster (minimum = 10). The stereotaxic coordinates are measured in millimetres, and gyral location and Brodmann areas (BA) were determined through criteria outlined in Talairach and Tournoux (1998).

Figure captions

Figure 1. Brain-behaviour correlation profile and corresponding singular image for LV1
a) LV1 brain-behaviour correlation profile separated by task. The correlation profile indicated that activity in negative salience brain regions correlated positively with age, reserve, and accuracy (ACC) during easy encoding events, and correlated positively with ACC during easy retrieval events. Error bars represent 95% confidence intervals. b) Singluar image for LV1 showing negative voxel saliences (cool coloured regions). The scale represents the range of bootstrap ratio values thresholded at ± 3.28, $p < 0.001$. Activations are presented on template images of the lateral and medial surfaces of the left and right hemispheres of the brain using Multi-image Analysis GUI (Mango) software (http://ric.uthscsa.edu/mango/).

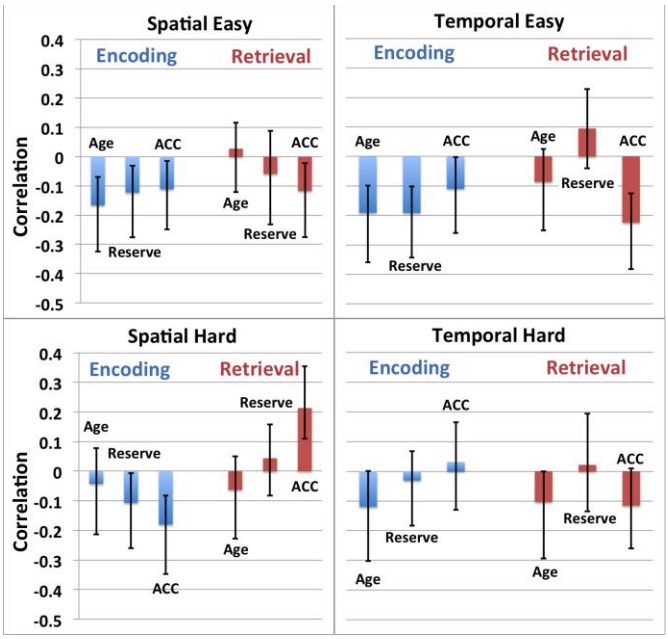
Figure 2. Brain-behaviour correlation profile and corresponding singular image for LV2
a) LV2 brain-behaviour correlation profile separated by task. The correlation profile indicated that activity in positive salience regions increased with age across task conditions and was negatively correlated with reserve at encoding (except for spatial easy). Activity in negative salience regions decreased with age across tasks and was positively correlated with reserve at encoding (except for spatial easy). ACC is short for accuracy, and error bars represent 95% confidence intervals. b) Singluar image for LV2 showing positive voxel saliences (warm coloured regions) and negative voxel saliences (cool coloured regions). The scale represents the range of bootstrap ratio values thresholded at ± 3.28, $p < 0.001$. Activations are presented on template images of the lateral and medial surfaces of the left and right hemispheres of the brain using Multi-image Analysis GUI (Mango) software (http://ric.uthscsa.edu/mango/).

Figure 3. Brain-behaviour correlation profile and corresponding singular image for LV3
a) LV3 brain-behaviour correlation profile separated by task. The correlation profile indicated that activity in positive salience regions increased with age at retrieval and decreased with age at encoding, and was positively correlated with reserve during spatial retrieval. Activity in negative salience regions increased with age at encoding and decreased with age at retrieval, and was negatively correlated with reserve during spatial retrieval. ACC is short for accuracy, and error bars represent 95% confidence intervals. b) Singluar image for LV3 showing positive voxel saliences (warm coloured regions) and negative voxel saliences (cool coloured regions). The scale represents the range of bootstrap ratio values thresholded at ± 3.28, $p < 0.001$. Activations are presented on template images of the lateral and medial surfaces of the left and right hemispheres of the brain using Multi-image Analysis GUI (Mango) software (http://ric.uthscsa.edu/mango/).

Figure 4. Brain-behaviour correlation profile and corresponding singular image for LV4
a) LV4 brain-behaviour correlation profile separated by task. The correlation profile indicated that activity in negative salience regions decreased with reserve across all retrieval events and increased with age during easy retrieval events. ACC is short for accuracy, and error bars represent 95% confidence intervals. b) Singluar image for LV4 showing negative voxel saliences (cool coloured regions). The scale represents the range of bootstrap ratio values thresholded at ± 3.28, $p < 0.001$. Peak activations were predominantly on the left and right lateral surfaces of the brain and were displayed using Multi-image Analysis GUI (Mango) software (http://ric.uthscsa.edu/mango/).

Figure 1.

a)


Spatial Easy
Temporal Easy
Spatial Hard
Temporal Hard
Encoding
Retrieval
Correlation
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
Age
Reserve
ACC

b)

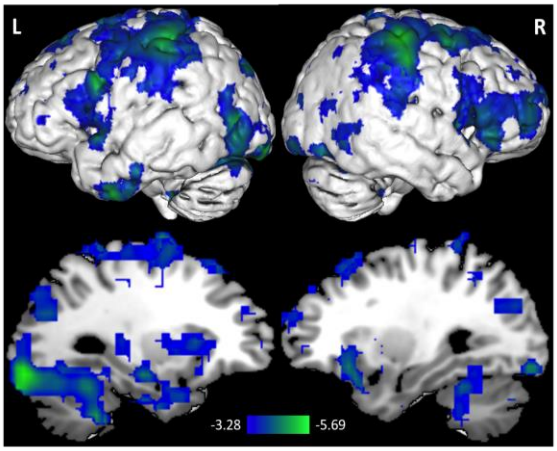

L
R
-3.28
-5.69

Figure 2.

a) b)

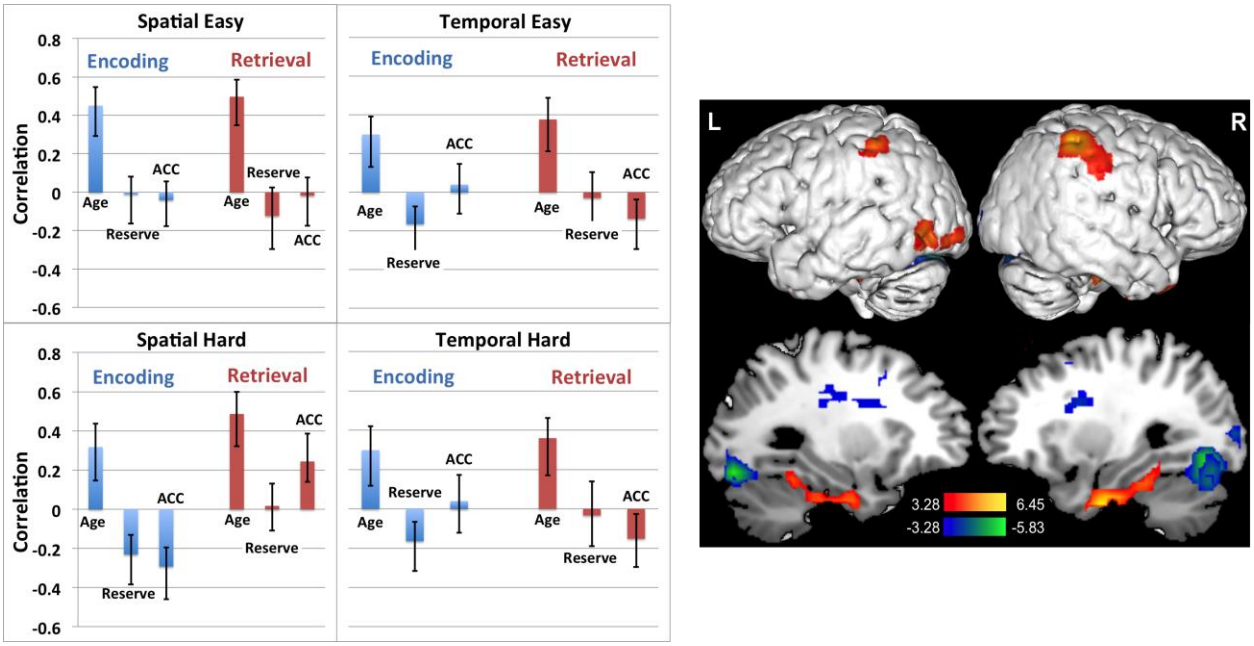

Spatial Easy
Temporal Easy
Spatial Hard
Temporal Hard
Encoding
Retrieval
Correlation
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
Age
Reserve
ACC
L
R
3.28
6.45
-3.28
-5.83

Figure 3.

a) b)

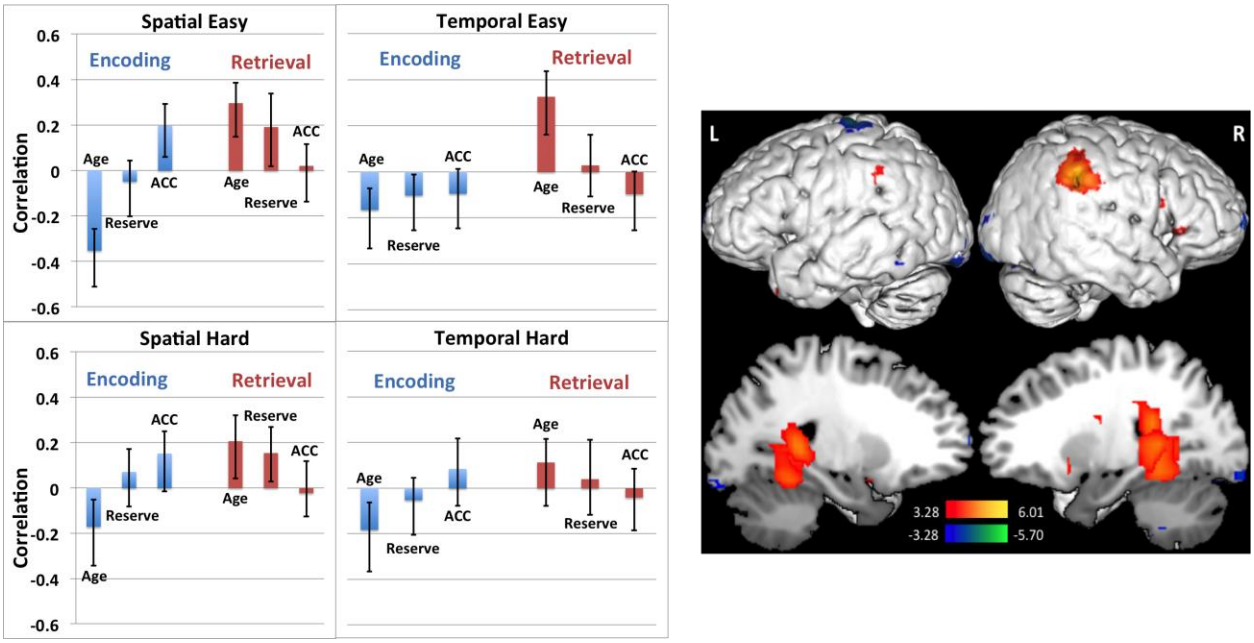
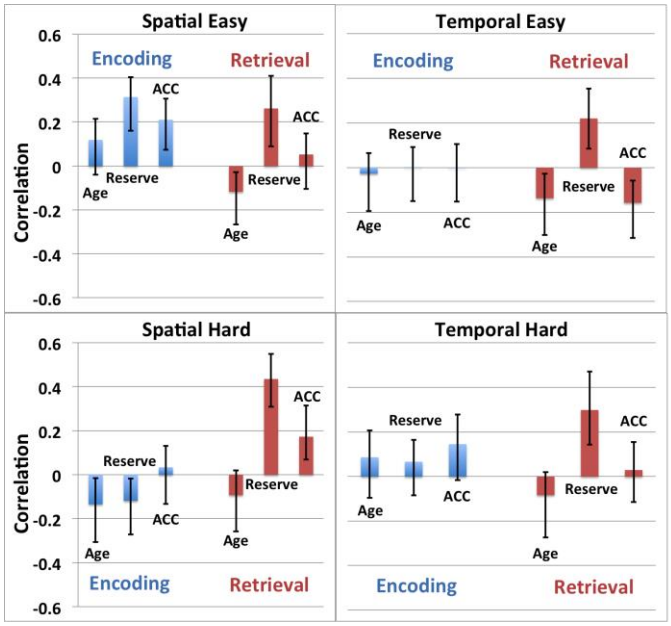
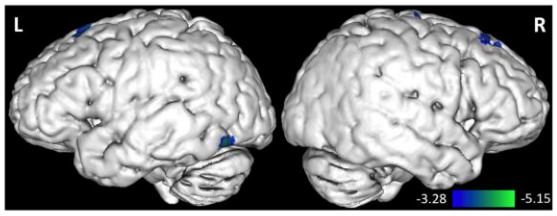

Spatial Easy
Temporal Easy
Spatial Hard
Temporal Hard
Encoding
Retrieval
Correlation
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
Age
Reserve
ACC
L
R
3.28
6.01
-3.28
-5.70

Figure 4.

a) b)


Spatial Easy
Temporal Easy
Spatial Hard
Temporal Hard
Encoding
Retrieval
Correlation
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
Age
Reserve
ACC


L
R
-3.28
-5.15