The association between cognitive reserve and performance-related brain activity during episodic encoding and retrieval across the adult lifespan

Running Head: Cognitive reserve and memory-related brain activity across the adult lifespan

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Abstract

Remembering associations between encoded items and their contextual setting is a feature of episodic memory. Although this ability generally deteriorates with age, there is substantial variability in how older individuals perform on episodic memory tasks. A current topic of debate in the cognitive neuroscience of aging literature revolves around whether 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 spanning a large adult lifespan sample (N=154), we tested whether higher cognitive reserve was associated with better task-fMRI context memory performance, and functional compensatory activity patterns in the aging brain. We used multivariate Behaviour Partial Least Squares (B-PLS) analysis to examine how age, retrieval accuracy, and a proxy measure of cognitive reserve (i.e., a composite score consisting of years of education [EDU] and crystallized IQ), impacted brain activity during the encoding and retrieval of spatial and temporal contextual details. The results indicated that age-related increases in encoding activity within anterior and lateral frontal, inferior parietal, occipito-temporal and medial temporal cortices, was correlated with better subsequent memory performance; and may be indicative of age-related functional compensation at encoding. Interestingly this compensatory pattern was not correlated with our proxy measure of cognitive reserve but was associated with total brain volume (a measure of brain reserve). However, cognitive reserve was associated with age-invariant and task-general activity in superior temporal, occipital, and left inferior frontal regions. We conclude that the relationship between cognitive reserve, brain reserve and age-related functional compensation is complex, and that EDU and IQ may not fully account for individual differences in cognitive reserve when studying well educated, healthy aging cohorts.

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, running into an acquaintance at the grocery store and trying to remember where we had initially met them. 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). Functional neuroimaging studies examining the neural underpinnings of successful context memory using face stimuli (i.e., face-location and/or temporal recency decisions) in younger adults (YA) have demonstrated that successful context memory relies on the activation of brain regions related to face processing (i.e., posterior ventral visual regions), prefrontal cortex (PFC), the hippocampus and surrounding medial temporal lobe (MTL) cortices, and parietal cortical regions (DuBrow & Davachi, 2014; Rajah et al., 2008, 2010; Sweegers & Talamini, 2014; Takashima et al., 2007, 2009).

In general, healthy aging is associated with a decline in cognitive functions (Park et al., 1996, 2002; Schaie, 2005). With respect to episodic memory, older adults (OA) show 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 OA are a homogenous group (Anderson et al., 2008; Cansino et al., 2013; Hashtroudi et al., 1989; McIntyre & Craik, 1987; Wegesin et al., 2000). Yet, there is significant variability in age-related context memory decline, and some OA perform comparably to YA on some memory tasks (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).

The ability of some OA to perform as well as YA on memory tasks may be explained by individual differences in *reserve* (Stern, 2002, 2012). The operational definitions of reserve, and closely related concepts, are still being developed and debated in the field today (Cabeza et al., 2018, 2019; Stern et al., 2018, 2019). In the current manuscript, we define reserve as the accrual of neural resources over one's lifetime, due to genetics and life experiences (environment), which help offset/attenuate the negative effects of age-related neural decline, and/or neuropathology, on cognitive function in later life (Cabeza et al., 20018; Stern et al., 2018). The concept of reserve has been developed to capture two sub-components, namely, brain reserve and cognitive reserve (Barulli & Stern, 2013; Stern, 2002; Stern et al., 2018). Brain reserve refers to the notion that morphological differences such as brain volume, number of neurons, dendritic branching, *etc.*, account for the differential susceptibility of individuals to cognitive decline as a function of age-related changes and/or pathology (Stern, 2009). It has been suggested that when brain reserve falls below a certain threshold, cognitive decline manifests. Therefore, according to this notion, individuals with a larger brain reserve will have better memory performance and therefore reach the threshold for functional impairment at a later age. Indeed, there is evidence suggesting that older adults with larger brain volumes have a reduced risk of developing dementia (Katzman et al., 1988; Schofield et al., 1997; Stern, 2012).

The second component of reserve, known as cognitive reserve, refers to the individual differences in cognitive operations or processes that are shaped by life experiences, which allow some individuals to maintain cognitive function in the face of brain aging and/or pathology (Stern, 2002, 2012). There is evidence that some lifestyle and biological factors help support

cognition in late life, i.e. education, intelligence, participation in leisure activities, and occupational complexity. These variables are typically used as indirect proxy measures for cognitive reserve, and cross-sectional studies indicate that older adults who have high levels of these measures, exhibit better episodic memory performance (Angel, Fay, Bouazzaoui, Baudouin, & Isingrini, 2010; Lachman, Agrigoroaei, Murphy, & Tun, 2010). It has been hypothesized that having higher levels of these proxy measures of cognitive reserve may result in having greater neural capacity, which may reflect the availability and accessibility of more neurocognitive strategies to perform various behavioural tasks; greater flexibility in the engagement of different neurocognitive strategies; and, greater neural efficiency in the utilization of brain regions and networks (Barulli & Stern, 2013). In other words, in relation to fMRI measurements of brain activity, an individual with higher proxy measure of cognitive reserve may be able to show less recruitment of task-related regions to perform a given task without compromising performance (i.e., efficiency); be able to maximize recruitment of task-related regions under increasing demands (i.e., capacity); or be able to utilize alternate networks to maintain or improve performance (i.e., flexibility). The ability of some OA to recruit additional brain regions to maintain task performance in the face of increased task demands has been described as *functional compensation* (Cabeza et al., 2002; Cabeza & Dennis, 2013). In that regard, functional compensation may be thought of as enhanced neural flexibility.

Indeed, there is debate as to how the concepts of cognitive reserve, brain reserve and compensation relate to one another. One perspective is that compensation is a mechanism of cognitive reserve, and thus is dependent on cognitive reserve (Barulli & Stern, 2013). On the other hand, compensation has also been viewed as being distinct from cognitive reserve, as it doesn't place as much emphasis on individual differences in life histories per se, but instead

emphasizes one's ability to activate alternate brain networks to support task performance when task demands exceed available resources (Cabeza & Dennis, 2013). For example, it is possible that two individuals may have the same level of proxy measures of cognitive reserve (i.e. education and IQ) but differentially engage age-related compensatory mechanisms to support task performance; perhaps due to different experiences with the task presented or current availability of task-specific neural resources. Alternatively, one can also imagine a scenario where two people have different levels of cognitive reserve, yet similarly engage age-related compensatory mechanisms to support task performance; perhaps due to similar experience with the task and availability of task-specific neural resources.

Clearly the concepts of cognitive reserve and compensation are tightly bound. Cabeza and colleagues (2019) suggest that reserve may prime the brain to deploy compensatory mechanisms to cope with the adverse effects of normal and pathological aging on cognitive function. Consistent with this hypothesis, previous studies have shown differential recruitment of brain networks in OA with high, compared to lower levels of proxy measures of cognitive 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 healthy YA and OA. In YA, they found that education and memory performance were positively correlated with activity in medial temporal, ventral visual and parietal cortices, and negatively 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. A meta-analysis of 17 fMRI experiments from 5 selected papers examined the relationship between cognitive reserve proxies and brain activity patterns related to a variety

of cognitive tasks including episodic memory in healthy aging, Alzheimer's disease (AD), and mild cognitive impairment (MCI) (Colangeli et al., 2016). Using activation likelihood estimation analysis, results revealed that in healthy OA, but not in AD or MCI patients, cognitive reserve was associated with greater levels of activation in the anterior cingulate gyrus, precuneus, superior frontal gyrus, and dorsolateral PFC. Results from this meta-analysis are in line with findings from Springer et al. (2005) demonstrating a positive association between cognitive reserve proxies and fronto-parietal activation in healthy OA. Notwithstanding, other studies have found a different pattern of results.

In an extension of previously published findings, Steffener et al., (2011) investigated whether cognitive reserve modulates the relationship between performance on a delayed item recognition task, and functional activity in healthy younger and OA. The authors created a composite measure of cognitive reserve based on years of education and intelligence quotient (IQ), and used path analysis to test several models linking expression of task-related fMRI networks, task performance and cognitive reserve. Results revealed that higher cognitive reserve in both younger and OA was associated with reduced expression of a fronto-parietal network, which in turn attenuated expression of a secondary network involving the right parahippocampal gyrus (PHG). Less PHG activity was associated with better task performance in the OA group only. More recently, Stern et al. (2018) examined blocked and event-related task fMRI data from a variety of cognitive domains in 58 YA (aged 18-31) and 91 OA aged (51-71) and identified a general pattern of brain activation that varied with IQ, as measured by the North American Reading Test (NART; Nelson & Wilison, 1991). They found that increased activity in cerebellum, medial PFC, and bilateral superior frontal gyrus across all tasks was associated with having higher IQ. They also found that higher IQ was related to decreased activity in bilateral

middle and inferior prefrontal cortex PFC and bilateral inferior parietal cortex. Interestingly, expression of this general pattern of brain activation also accounted for additional variance in task performance after controlling for cortical thickness. This suggests that brain reserve moderates the relationship between cognitive reserve-related brain activity and cognitive performance.

Overall, findings from the studies discussed thus far present different patterns of results regarding how cognitive reserve may be related to age-related functional compensation. The results from Springer et al (2005) and Colangeli et al (2016) support the hypothesis that higher levels of cognitive reserve result in greater functional activity in fronto-parietal regions in healthy OA. This may reflect greater neural capacity and flexibility in these OA. In contrast, Steffener et al. (2011) and Stern et al. (2018) observed reduced PFC and parietal activity with higher reserve. These findings suggest that higher cognitive reserve may relate to greater neural efficiency. One possible explanation for these opposing results was presented by Stern et al. (2018). They suggested that at lower levels of task difficulty, cognitive reserve may manifest as enhanced neural efficiency in fMRI studies, and at higher levels of task difficulty, cognitive reserve may present as enhanced activity/capacity. However, it remains unclear if these reserve-related patterns of activity are similar across the adult lifespan, if task difficulty modulates the patterns observed, and whether they directly benefit memory performance. In other words, it remains unclear if there is a positive association between proxy measures of cognitive reserve and increases or decreases in brain activity to support performance on a variety of episodic memory tasks, at varying levels of difficulty, across the adult lifespan. In the current study we test this hypothesis.

In this study, 154 adults between the ages of 19-76 years underwent neuropsychological testing and fMRI scanning during easy and difficult versions of left/right face-location spatial context memory tasks and least/most recent face temporal context memory task. FMRI scans were obtained during both encoding and retrieval. Initial analyses that explored age and performance-related patterns of brain activity in a subset of this dataset (N = 128) have been previously published (Ankudowich et al., 2016, 2017). Here, we tested 26 more adults in this experimental paradigm. We calculated a proxy measure of cognitive reserve, based on years of education and performance on the AMNART (Grober & Sliwinski, 1991). We then tested the hypothesis that cognitive reserve moderated the effect of age on our measures of episodic memory function obtained from task fMRI and used multivariate Behavioural Partial Least Squares (B-PLS) to examine how age, cognitive reserve, and memory performance related to brain activity at encoding and retrieval across the adult lifespan. We predicted that if having greater cognitive reserve was positively associated with one's ability to engage prefrontal, parietal and medial temporal functional compensatory mechanisms (Ankudowich et al., 2017; Cabeza et al., 2002; Colangeli et al., 2016; Springer et al., 2005), then activity in these regions would be positively correlated with age, cognitive reserve and memory performance, and post-hoc regression analyses on this pattern of brain activity would yield a significant age*cognitive reserve interaction.

2. Methods

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

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, SD = 3.51; 28 females; EDU = 16.21 yrs, SD = 1.91, EDU range = 11-20 yrs), 68 were middle-aged (age range 40-58 yrs, mean age = 50.00 yrs, SD = 5.33; 51 females; EDU = 15.35 yrs, SD = 2.02, EDU range = 11-20 yrs), and 44 were old (age range 60-76 yrs, mean age = 66.39 yrs, SD = 3.69; 30 females; EDU = 15.61 yrs, SD = 2.42, EDU range = 11-20 yrs). This sample size is adequately powered to examine age, performance and reserve effects based on prior simulation studies conducted to establish necessary sample sized in task fMRI (Desmond & Glover, 2002; Mumford & Nichols, 2008). 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 to participate in the fMRI session. The measures consisted of the Folstein Mini Mental State Examination (MMSE), exclusion cut-off < 27 (Folstein et al., 1975); the Mini-International Neuropsychiatric Interview [MINI], inclusion cutoff =/< 2 (Sheehan et al., 1998); the Beck Depression Inventory (BDI-II), exclusion cut-off > 13 (Beck et al., 1996). Legal copyright restrictions prevent public archiving of the questionnaires, which are available from the cited references for each measure. Additional medical exclusion criteria included: having a lifetime history of a substance abuse, psychiatric illness, neurological illness or insult (i.e. stroke, concussion, traumatic brain injury), having a lifetime 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 and medical inclusion criteria and performed above chance on the mock-MRI scanner trials, were invited to participate in a second fMRI testing session. All participants self-reported as being in good health at the time of the fMRI scan. We calculated a proxy measure of reserve for each participant by calculating the mean value of z-scored education in years and z-scored estimated IQ based on the AMNART. 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. The conditions of our ethics approval do not permit sharing of the data supporting this study with any individual outside the author team under any circumstances.

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 (see Figure 1).

The task stimulus set has been used in previous studies (Rajah et al., 2008, 2010), and consisted of black and white photographs of age variant faces. 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. The task program code and stimulus set used are made publicly available (Rajah et al., 2020b).

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 were 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

SPSS version 24 (IBM Corp., 2016) was used to conduct repeated-measures mixed effects ANOVAs on retrieval accuracy (% correct) and reaction time (msec) with group (3: young, middle-aged, older adults) as a between-subjects factor, task (2: spatial, temporal) and difficulty (2: easy, hard) as within-subject factors, and sex (2: male, female) as a covariate to determine significant group, task and difficulty main effects, and interactions (significance threshold $p < 0.05$) while controlling for sex-related effects. Post-hoc tests were conducted as needed to clarify significant effects and interactions. The SPSS analysis script used is made publicly available (Rajah et al., 2020e)

Regression analysis

To test the hypothesis that reserve moderated the effect of age on the task fMRI accuracy and RT measures, we used linear regression implemented in R (R Core Team, 2014) to test the following models: $DV \sim \beta + Age + Reserve + Age*Reserve + \varepsilon$, in which DV = mean accuracy on SE, SH, TE and TH tasks; and mean RT for SE, SH, TE and TH tasks. Significance assessed at $p < 0.05$ corrected for multiple comparisons. The R-code used to conduct this analysis is made publicly available (Rajah et al., 2020d)

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. One participant had > 4mm movement and was

excluded from further analysis. Functional images were then spatially normalized to the Montreal Neurological Institute (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

We conducted a Multivariate Behavioural PLS (B-PLS; https://www.rotman-baycrest.on.ca/index.php?section=84) analysis to identify how whole brain patterns of activity varied as a function of age, reserve, and/or task accuracy at encoding and retrieval. We selected B-PLS for our analyses 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 scripts used to conduct the B-PLS analysis are made publicly available (Rajah et al., 2020c). The first step in B-PLS 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) (McIntosh et al., 2004). The rows of the 2D data matrix reflect the following experimental conditions nested within subjects: SE encoding, SH encoding, TE encoding, TH encoding, SE retrieval, SH retrieval, TE retrieval, TH retrieval. The columns of the fMRI data matrix reflect the event-related activity for each brain voxel, at each time point, for correctly encoded and retrieved events. For each event, activity was included for seven time-points/measurements,

equivalent to 7 TRs (TR = 2 sec * 7 = 14 sec of activity per event), following the event onset. Thus, the first column of the data matrix reflected brain activity at event onset; the second column of the data matrix reflected activity at 2 sec following the event onset; the third column of the data matrix reflected activity at 4 sec following the event onset; and so forth. To control for low frequency signal drifts due to environmental and/or physiological noise (McIntosh et al., 2004), event-related activity was base-line corrected (zeroed) to the event onset. The event-related brain activity is then mean-centred within condition. As such, the data matrix reflected mean corrected percent change in brain activity from event onset for all conditions, stacked within subjects.

The fMRI data matrix was then cross-correlated with three behavioural vectors stacked in the same condition, nested within subject order: age, proxy measure of reserve (reserve), and mean retrieval accuracy per condition. The mean retrieval accuracy included in the analysis was orthogonalized to the age variable by obtaining its residual from a linear regression in which age was the predictor. This was done because age and raw accuracy were correlated. 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 the three behavioural 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 each of the three 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 for each B-PLS analysis. The permutation test involved sampling without replacement to reassign links 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).

In order to determine at which time lags the correlation profile in a given LV was strongest, we computed temporal brain scores for each significant LV. Temporal brain scores

reflect how strongly each participant's data reflected 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. To confirm our interpretations of the effects represented in each significant LV, we ran post-hoc general linear model (GLM) comparisons on the brain scores for the task conditions against our three behavioural vectors of interest while controlling for the effects of total grey matter volume. We chose to control for total grey matter volume in our analysis following recommendations outlined by Reed et al. (2010) and implemented by others (e.g., Stern, et al., 2018). Reed et al. (2010) recommends regressing out the effects of structural variables known to impact cognitive decline (e.g., total grey matter volume, white matter hyperintensities etc.) and then to examine whether the residual reserve component moderates cognitive function. This allows for examining the effects of reserve on cognitive function above and beyond what could be predicted by structural decline. To extract total brain volumes of each subject, we used the Corticometric Iterative Vertex-based Estimation of Thickness (CIVET) pipeline (described in supplementary material). Since age and total grey matter volumes showed a strong negative correlation ($p < .001$), we orthogonalized total grey matter volumes to the age variable by obtaining the residual from a linear regression in which age was the predictor. This total grey matter volume residual variable was then used as a

covariate in our post-hoc GLM analysis to confirm our interpretations of each LV while controlling for the effects of brain volume.

3. Results

3.1 Behavioural results

Table 1 summarizes demographics, neuropsychological test data, and context memory performance for all groups. One-way ANOVAs indicated that both young and OA had higher reserve compared to middle-aged adults ($F(2,151) = 3.503$, $p < 0.033$, $\eta 2 = 0.044$). On, the CVLT delay free recall, YA outperformed middle-aged adults ($F(2,151) = 3.94$, $p = 0.021$, $\eta 2 = 0.050$), and completed more categories on the WCST ($F(2,151) = 13.73$, $p < 0.001$, $\eta 2 = 0.154$) than both middle-aged and OA. YA were also more accurate on the WCST ($F(2,151) = 12.96$, $p < 0.001$, $\eta 2 = 0.146$) than both middle-aged and OA. On the D-KEFS category fluency, OA 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 ($F(2, 150) = 22.12$, $p < 0.001$, $\eta 2 = 0.228$), task ($F(1, 150) = 618.90$, $p < 0.001$, $\eta 2 = 0.805$), difficulty ($F(1, 150) = 107.06$, $p < 0.001$, $\eta 2 = 0.416$), and a task x difficulty interaction ($F(1, 150) = 32.35$, $p < 0.001$, $\eta 2 = 0.177$). There was no significant main effect or interactions of sex. Tukey's HSD post-hoc test indicated that the significant main effect of group was due to YA outperforming both middle-aged and OA, and middle aged adults outperforming OA 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). We did not observe an overall age*difficulty interaction in the current study. This may be since the temporal context memory task was challenging to all age-groups. Exploratory repeated one-way ANOVAs examining age and difficulty effects within task-type verified this interpretation. For the temporal context memory tasks, we observed significant main effects of age-group (F (2, 151) = 22.66, p<0.001) and difficulty (F (1,151) =116.72, p<0.001), but no significant age*difficulty interaction. However, for the spatial context memory tasks we observed a significant age*difficulty interaction (F (2,151) = 4.08, p< 0.05); and, significant main effects of age-group (F (2,151) = 12.89, p<0.001) and difficulty (F (1, 151) = 20.12, p<0.001).

Within-age group and across-age group correlations between reserve and retrieval accuracy for each task (i.e., SE, SH, TE, and TH) failed to reach significance threshold for any of the tasks.

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, 150) = 12.90, p < 0.001, $\eta 2$ = 0.147), task (F (1, 150) = 154.83, p < 0.05, $\eta 2$ = 0.508), and difficulty (F (1, 150) = 29.05, p < 0.05, $\eta 2$ = 0.162). There was no significant main effect or interactions of sex. Tukey's HSD post-hoc test indicated that YA responded faster than both middle-aged and OA 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).

3.1.3 Regression analyses results

The regression models with task accuracy and reaction times for each of the task conditions (SE, SH, TE, TH), as dependant variables, and age, cognitive reserve, and

age*cognitive reserve as predictors, did not yield any significant main effects of cognitive reserve, or age*cognitive reserve interactions. However, age was a significant predictor for all the models indicating that task performance decreased with advanced age. The lack of a main effect of cognitive reserve or age*cognitive reserve interaction indicates that our proxy measure of cognitive reserve did not modulate memory performance.

3.2 fMRI results

The B-PLS analysis revealed five significant LVs linking whole-brain patterns of activity to the behavioural vectors of age, reserve, and task accuracy (residualized by age). LV1 accounted for 19.76% 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 2a shows the PLS correlation profile separated by task (SE, SH, TE, and TH), and the corresponding singular image presented in Figure 2b 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 was also correlated positively with subsequent accuracy, (but not with reserve) 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, and subsequent retrieval accuracy during easy encoding events, and increased with retrieval accuracy during easy retrieval events.

The post-hoc GLM for brain scores within easy encoding events against age, cognitive reserve, task accuracy, and total grey matter volume (R^2 = 0.08, F (15, 288) = 1.75, p = .04) revealed a significant main effect for age ($p < 0.05$), but not for accuracy or cognitive reserve. Interestingly, re-running the post-hoc GLM within easy encoding events against age, cognitive reserve, and task accuracy without controlling for total grey matter volumes (R^2 = 0.08, F (7, 296) = 2.70, p = .009), revealed significant main effect for both age and accuracy (ps < .05), consistent with our interpretation of this LV. On the other hand, post-hoc GLM for brain scores within easy retrieval events for all three variables (R^2 = 0.08, F (15, 288) = 1.73, p = .04) revealed a significant main effect for task accuracy only ($p < 0.001$). There were no significant age*cognitive reserve, age*accuracy or any other significant interactions revealed by the post-hoc tests. The negative salience brain regions represented in LV1 included: bilateral fusiform gyrus, medial frontal extending to ventrolateral PFC (BA 6/44), bilateral anterior PFC (BA 9/10), inferior parietal lobule (IPL), left frontal eye-fields (FEF: BA 8), left anterior temporal cortex, left hippocampus, and other regions (see Table 2).

LV2 accounted for 11.86% 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 and decreases of activity with age across all encoding and retrieval events. The post-hoc GLM for brain scores against age, cognitive reserve, task accuracy, and total grey matter volume (R^2 = 0.18, F (15, 1200) = 17.79, p < .001) revealed a significant main effect for age across task conditions ($p < 0.001$), confirming this interpretation. The PLS correlation profile and the corresponding singular image are presented in Figures 2c and 2d 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 28); and negatively correlated with

activity in left fusiform cortex, posterior cingulate and thalamus. While some of the effects represented in this LV might be attributed to accuracy as shown in the PLS correlation profile, the effects observed resemble 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 9.52% of the total cross-block covariance ($p < 0.001$). This LV 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 are presented in Table 4. The PLS correlation profile and the corresponding singular image for LV3 are presented in Figures 3a and 3b respectively. Based on the PLS correlation profile, activity in positive salience brain regions (warm coloured regions in Figures 3b) were positively correlated with age during retrieval conditions (except TH retrieval), and negatively correlated with age at encoding. Positive salience brain regions included: bilateral hippocampus, IPL, putamen, superior temporal gyrus, and right ventrolateral PFC (BA 44). In contrast, activity in negative salience regions (blue coloured regions in Figures 3b) were positively correlated with age across all encoding conditions, and negatively correlated with age during retrieval. These regions included: bilateral fusiform gyrus, left postcentral gyrus, precuneus, and right precentral gyrus. Post-hoc GLMs for brain scores against age, cognitive reserve, task accuracy, and total grey matter volume at encoding ($R^2 = 0.09$, $F(15, 592) = 3.95$, $p < .001$), and retrieval ($R^2 = 0.06$, $F(15, 592) = 2.64$, $p < .001$), revealed significant main effects of age ($ps < 0.01$), but in opposite directions, mirroring the age x phase interaction outlined in the PLS correlation profile.

LV4 accounted for 6.94% of the total cross-block covariance ($p < 0.001$) and identified a pattern of brain activity that was mainly related to cognitive reserve across task conditions. The local maxima of negative and positive salience brain regions are presented in Table 5. Based on

the PLS correlation profile (Figure 3c) and the corresponding singular image (Figure 3d), across all encoding and retrieval tasks (except SH encoding), activity in left superior temporal, caudate, and right cuneus increased with reserve. In contrast, activity in left dorsolateral PFC (BA 9) decreased with cognitive reserve. The post-hoc GLM model testing for brain scores against age, cognitive reserve, task accuracy, and grey matter volume across task conditions (R^2 = 0. 13, F (15, 1200) = 12.42, p < .001) revealed a significant main effect of cognitive reserve (p < 0.001), confirming our interpretation.

The last significant LV (LV5) accounted for less than 5% of the total cross-block co-variance and showed minimal effects related to age, cognitive reserve, or accuracy, rending it uninterpretable. For this reason, LV5 will not be discussed further.

Exploratory cortical thickness analysis

Given that our current results revealed that cognitive reserve (as defined by EDU and IQ) does not modulate memory performance or moderate the effect of age on context memory-related fMRI activity in our sample, we were interested in exploring whether our measure of cognitive reserve moderates the relationship between age and cortical thickness in our sample. To that end, we processed T1-weighted structural scans of our 154 participants using the CIVET pipeline (described in supplementary material) for cortical thickness estimation. Two scans failed quality assurance using the pipeline, resulting in a total sample size of 152 scans. A whole brain vertex-wise regression analysis of cortical thickness was conducted, with age, and our proxy measure of cognitive reserve in the GLM while controlling for the effects of sex. Main effects and interactions we tested and False Discovery Rate (FDR) correction was to adjust for multiple comparisons. Results showed a strong main effect of age in primarily temporal and parietal regions. Age was negatively correlated with cortical thickness in those areas. There was also a

main effect of sex where females had reduced cortical thickness compared to males in primarily sensorimotor regions of the cortex. Results are displayed as t-maps surviving 5% and 1% FDR in supplementary Figure 1. We did not observe a main effect of cognitive reserve or any interactions. Therefore, our results suggest that cognitive reserve does not moderate effect of age on cortical thickness in our sample.

4. Discussion

In the current adult lifespan task fMRI study, we tested the hypothesis that higher levels of cognitive reserve with increasing age would be related to better context memory performance, as well as modulations in task-related brain activity in prefrontal, medial temporal and parietal cortices to support performance on spatial and temporal context memory tasks at varying levels of difficulty. To test this hypothesis, we created a proxy measure of cognitive reserve that included levels of educational attainment and intelligence (AMNART-IQ). We then conducted a B-PLS analysis to examine how age, cognitive reserve, and retrieval accuracy correlated with brain activity during easy and hard, spatial and temporal context memory encoding and retrieval tasks. We also conducted an exploratory cortical thickness analysis to examine whether our proxy measure of cognitive reserve moderates the relationship between age and cortical thickness in our dataset.

The behavioural regression analysis revealed that greater levels of cognitive reserve, as measured by education and IQ, did not predict task-fMRI context memory performance in our adult lifespan sample. However, our regression and ANOVA 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 et al., 2004; Wegesin et al., 2000). Participants in the current study also showed higher accuracy on easy relative to hard tasks, implying that increasing encoding load increased task difficulty.

The fact that we did not find a significant association between cognitive reserve and memory performance, and age-related memory declines is consistent with previous findings (Zahodne et al., 2011). However, some cross-sectional studies have shown a positive association between reserve proxies and episodic memory performance across age (Angel et al., 2010; Corral, Rodriguez, Amenedo, Sanchez, & Diaz, 2006; Lachman et al., 2010). The inconsistency between the current results and the aforementioned studies may partly be due to methodological differences. For example, Corral et al. (2006) and Angel et al. (2010) categorized participants into high vs. low reserve groups, unlike the current study which examined cognitive reserve and episodic memory performance as continuous variables. It is also likely that our strict inclusion criteria may have contributed to skewing our sample towards individuals with higher levels of education. Our current sample included participants with years of education ranging from 11-20 years, which suggests the sample consisted of relatively highly educated individuals. In contrast the study by Angel et al. (2010) included a sample with years of education ranging from 8-17 years. It is possible that inclusion of more individuals with lower levels of education may help adequately capture the positive relationship between reserve and episodic memory performance.

In relation to the fMRI findings, the B-PLS analysis identified effects linking brain activity and age across all task conditions (LV 2), and brain activity and age-by-phase (encoding and retrieval) interactions (LV 3). We have observed similar results in our prior analyses of a subset of this dataset (Ankudowich et al., 2016, 2017) and have interpreted these results in our prior publications. In general, findings from LVs 2 and 3 are largely consistent with observations

from previous fMRI studies of episodic memory across the adult lifespan and show that 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). In addition, we identified two additional LVs: one that identified brain regions in which encoding activity correlated with age and subsequent memory (LV1), and one that identified brain regions in which activity correlated with our proxy measure of cognitive reserve (LV4). We discuss each of these LVs in detail in the sections below.

Age- and performance-related patterns of brain activity: Evidence for encoding related compensation

The first LV (LV1) revealed that encoding activity in bilateral ventrolateral and right dorsolateral PFC, bilateral MTL (including the hippocampus), inferior parietal, precuneus and ventral occipito-temporal activity during easy tasks, was positively correlated with age and subsequent memory. During retrieval, activity in these same regions was correlated with retrieval accuracy during easy tasks; however, this was not correlated with age or cognitive 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)

Of interest here, is that we observed an age-related increase in encoding activity that was correlated with better subsequent context memory performance, and was apparent in presence of grey matter volume loss; and thus may reflect functional compensation in the aging brain.

Notably, this age-related compensatory effect was only observed during easy tasks. This is consistent with predictions of the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) and Scaffolding Theory of Aging and Cognition (STAC), which suggest that load-sensitive, task-related brain regions are recruited in older age at lower levels of task demands compared to young adults 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.

Specifically, in LV1, we observed age-related increases in left anterior hippocampal activity at encoding. The anterior hippocampus has been shown to be more active during episodic encoding, compared to retrieval (Kim, 2015; Lepage et al., 1998) and to contribute to relational processes (Davachi, 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 have also shown that age-related reduction in anterior hippocampal volumes was associated with increased encoding activity in occipital, lateral temporal and PFC, and better subsequent memory for easier, compared to harder, context memory task (Maillet & Rajah, 2013). The current results corroborate our prior findings and indicate that older individuals were better able to co-activate anterior hippocampal, occipital-temporal and PFC regions at encoding to support performance during easy tasks.

LV1 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-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 et al., 2014). Taken together, our findings indicate that OA may be able to recruit frontoparietal cognitive control processes to modulate the engagement of the aforementioned visual and mnemonic strategies as a form of compensation for age-related deficits and support memory performance during easy context memory tasks.

Interestingly, we did not observe significant correlations between activity in LV1 and our proxy measures of cognitive reserve. This observation is consistent with our behavioural results showing no significant association between context memory retrieval accuracy and our proxy measure of cognitive reserve; and our exploratory structural analysis showing no significant moderation of age-related cortical thinning by cognitive reserve. We interpreted our null behavioural effects, as potentially reflecting the high level of education and IQ in our sample, and limited range in our proxy measure of reserve. This explanation may also account for the lack of associations between activity in LV1 and our proxy cognitive reserve, even after controlling for total brain volume. However, the fact that our fMRI analysis identified a unique

pattern of brain activation that related to cognitive reserve, suggests that null effects observe in LV1 may not be related to restricted range or ceiling effects. Alternatively, it is possible that the current proxy measure of cognitive reserve, which correlated with activity in brain regions important for semantic memory (see below; (Rissman & Wagner, 2012), did not adequately capture cognitive processes important for the spatial and temporal context memory tasks used in the current study. For instance, it could be that if we used as a measure of cognitive reserve that may correlate with one's life experience with faces and other social stimuli i.e. social engagement (Conroy et al., 2010; Hertzog et al., 2008) or extraversion (Pichet Binette et al., 2020), then there would have been a correlation between our proxy measure of cognitive reserve and the pattern of age-related compensatory activity observed in LV1. This suggests that to see a correlation between cognitive reserve and compensatory activation, the demands of a given task should align with the processes being 'tapped into' by the proxy measures used to measure cognitive reserve. However, this explanation is post-hoc and highly speculative.

Interestingly, in our post-hoc B-PLS analyses we found that when total grey matter volume was included in the regression model examining the association between LV1 brain scores, age, memory performance and cognitive reserve; only age significantly predicted LV1 brain scores. However, when total grey matter volume was not included in this regression, both age and accuracy were significant predictors of LV1 brain scores. These results suggest that there may be an indirect association between accuracy, brain volume and brain activity in areas identified in LV1. Given that total brain volume is a measure of structural brain reserve, these post-hoc analyses suggest that compensatory activation in LV1 may be indirectly correlated with brain reserve (Stern et al., 2018; Stern et al., 2003).

Neural correlates of cognitive reserve

LV4 identified brain regions in which task-related activity was correlated with cognitive reserve, but not age and retrieval accuracy. Specifically, this LV identified a significant correlation between increases in left superior temporal and cuneus activity, and decreases in left inferior frontal activity, and cognitive reserve across task conditions. This suggest that individual differences in cognitive reserve was related to differential activity in brain regions important for semantic processing (Rissman & Wagner, 2010). However, activity in these reserve-related brain regions was not correlated with face-location spatial context memory performance and age in the current study.

It has been suggested that the neural implementation of reserve manifests as a domain-general pattern that is expressed across a variety of cognitive tasks and that the degree of expression of this pattern would correlate with reserve proxies like education and IQ (Cabeza et al., 2018). The current findings are consistent with this notion and demonstrate that cognitive reserve (as indexed by education and crystallized IQ) was associated with linear increases and decreases in brain activity across easy and hard spatial/temporal context memory, both during encoding and retrieval. Stern and colleagues (2018) used a multivariate analysis approach to identify a task-general pattern of activity that correlates with a proxy of cognitive reserve (NART-IQ) in individuals aged 20-80 years old. Across 12 different cognitive tasks including episodic memory, they found that activity in several regions including cerebellum, medial frontal and superior temporal regions increased with cognitive reserve, while activity in inferior frontal and parietal regions decreased with cognitive reserve, consistent with the current results. Similar to arguments made by Stern et al., (2018), we propose that this pattern of activity related to cognitive reserve is available throughout the adult lifespan and may set up individuals to deal with age-related changes as they occur in old age. This suggestion is also in line with the concept

of 'neural reserve' which posits that individual differences in brain networks modulated by cognitive reserve may allow some individuals to cope with the disruption related to age or brain pathology (Stern, 2009).

Conclusion

Recent reviews have theorized how the concepts of cognitive reserve, brain reserve and compensation may relate to one another and support resilience in the aging brain (Cabeza et al., 2018; Stern, et al., 2018). One view argues that higher cognitive reserve helps mitigate age-related neurocognitive decline in older age by improving older adults' ability to engage functional compensatory brain networks; in addition to enhancing one's neural efficiency and neural capacity (Stern, 2009; Stern, et al., 2018, 2018). Alternatively, it has been suggested that compensation and cognitive reserve may be related, but distinct, neurocognitive mechanisms that support cognition in later life. In other words, reserve may be necessary, but not sufficient for age-related functional compensation to occur (Cabeza et al., 2018, 2019). Our current study findings contribute to this debate and advance our understanding of how education and IQ, common proxy measures of cognitive reserve, relate to brain reserve, and age-related functional compensation during episodic memory tasks.

Specifically, we found that age-related functional compensation during our episodic memory tasks was indirectly influenced by *brain* reserve, as measured by total brain volume, but was not significantly correlated with a proxy measure of *cognitive* reserve that included education and IQ (LV1). Moreover, our proxy measure of cognitive reserve was not significantly associated with cortical thickness. Yet, adults with higher cognitive reserve activated brain regions associated with semantic memory across all tasks, and this pattern of brain activity was not correlated with age or task performance. Therefore, in the current study, the proxy measure

of cognitive reserve was not strongly related to either brain reserve, episodic memory task performance or age-related functional compensation. This result indicates that education and IQ may not be good proxy measures of cognitive reserve in a high functioning healthy sample of adults. This is surprising since education and crystallized intelligence are two of the most commonly used proxy measures of cognitive reserve. However, these measures only represent a narrow aspect of reserve and may fail to capture the breadth of the environmental and genetic factors that make up reserve. Therefore, the compensatory pattern of activity observed in LV1 in the current study may have been driven by other genetic and/or lifestyle factors that may have directly influenced brain reserve, but not cognitive reserve – as measured in the current study. It is thus important that other proxy factors such as occupational complexity, social interaction, leisure, physical activity and other protective factors should be taken into account when examining the impact of reserve on cognitive performance, and/or brain structure and function. In conclusion, it is important that researchers explore additional proxy measures of cognitive reserve, beyond education and IQ, when studying healthy high-functioning adult samples and define *a priori*: i) what their proxy measure of cognitive reserve is, ii) why it was selected and ii) whether the processes measures by these proxy measures relate the outcome measure/task being used – perhaps then, we may expect to see a correlation between cognitive reserve and age-related functional compensation during task performance.

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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%]		
Cognitive reserve composite [a]	0.26 (0.13)	-0.20 (0.12)	0.16 (0.15)	.033*	.044
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 (AMNART)	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; AMNART = 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, and task accuracy

Hemisphere	Temporal lag	Bootstrap ratio	Spatial extent	Talairach coordinates			Gyral location	BA
				x	y	z		
Negative Saliences: Increased activity with age, and subsequent accuracy during easy encoding events, and increased activity that predicted task accuracy during easy retrieval events								
Left								
	2,3,5	-6.23	2518	-2	-14	53	Medial frontal	6
	4	-5.92	4498	-31	-79	15	Fusiform	18
	4,5	-5.57	2280	-39	-9	42	Middle frontal	6
	2,3	-5.53	231	-45	-10	-23	Inferior temporal	20
	2,3	-4.89	37	-16	-63	12	Posterior cingulate	30
	2	-4.75	212	-56	-40	44	Inferior parietal lobule	40
	5	-4.56	184	-30	-14	-23	Hippocampus	-
	2	-4.20	29	-53	-65	-6	Middle occipital	37
	3	-4.15	23	-16	2	1	Globus Pallidus	-
	4,5	-4.09	28	-16	-25	12	Thalamus	-
	2	-3.87	19	-53	9	8	Inferior frontal	44
	2	-3.80	22	-34	-34	-14	Parahippocampal	-
	2	-3.59	11	-31	-2	7	Putamen	
	2	-3.52	11	-9	-54	39	Precuneus	7
Right								
	2,3	-5.85	302	50	-32	42	Inferior parietal lobule	40
	3,4,5	-5.51	330	40	45	24	Middle/Superior frontal	9/10
	3	-4.89	92	47	2	45	Precentral	6
	5	-4.85	49	43	-64	-12	Fusiform	37
	2	-4.80	84	47	8	13	Inferior frontal	44
	3,5	-4.70	41	32	-83	-10	Middle/inferior occipital	18
	3	-4.52	63	47	8	17	Insula	13
	5	-4.40	18	29	-7	-25	Amygdala	-
	2	-4.11	11	28	-43	1	Hippocampus	-
	2	-3.83	14	13	-66	42	Precuneus	7
	5	-3.80	26	14	-6	8	Thalamus	-
	2	-3.74	13	13	-59	17	Posterior cingulate	30
	4	-3.65	12	43	-21	7	Insula	13

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			Gyral location	BA
				x	y	z		
Negative saliences: Decreased activity with age across task conditions								
Left								
	3,4	-6.18	223	-1	-30	23	Posterior cingulate	23
	2	-5.63	77	-27	-75	-14	Fusiform	19
	5	-4.62	162	-1	-7	14	Thalamus	-
	2	-4.49	112	-5	26	25	Anterior cingulate	24
	4	-4.15	48	-24	6	40	Middle frontal	6
	3	-3.99	12	-13	-64	30	Precuneus	7
	5	-3.91	21	-16	24	13	Caudate	-
Right								
	3	-3.99	12	-13	-64	30	Precuneus	7
	5	-3.91	21	-16	24	13	Caudate	-
Positive Saliences: Increased activity with age across task conditions								
Left								
	2,3	5.67	49	-61	-39	39	Inferior parietal lobule	40
	2	4.89	43	-57	-61	-6	Inferior temporal	37
	3,4	4.41	21	-46	-75	-11	Inferior occipital	18/ 19
	4	4.32	11	-24	27	57	Superior/middle frontal	6
	4	4.22	18	-30	12	-20	Inferior frontal	47
	3	4.15	53	-2	-18	57	Medial frontal	6
Right								
	2,3	6.33	140	54	-39	41	Inferior parietal	40
	4	5.06	678	18	-18	-22	Parahippocampal	28
	4	4.89	33	6	34	62	Superior frontal	6
	4	4.39	24	37	16	-30	Superior temporal	38

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			Gyral location	BA
				x	y	z		
Negative Saliences: Increased activity with age at encoding and decreased at retrieval								
Left								
	2,3,4,5	-5.39	107	-39	-34	62	Postcentral gyrus	1/2
	2	-4.80	20	-20	55	18	Middle frontal	10
	2,3	-4.60	42	-13	-72	30	Precuneus	7/13
	3	-4.04	37	-27	-75	-14	Fusiform	19
Right								
	3,4,5	-5.58	90	25	-87	-14	Fusiform	18/37
	4	-5.11	39	46	-11	58	Precentral	4/6
Positive Saliences: Increased activity with age at retrieval and decreased at encoding								
Left								
	5	4.69	64	-27	-43	7	Hippocampus	-
	2	4.40	42	-23	7	-6	Putamen	-
	2	3.65	14	-24	-30	26	Caudate	-
Right								
	3,5	5.87	1017	50	-35	31	Inferior parietal lobule	40
	4	5.12	610	25	-41	19	Caudate Tail	-
	5	4.55	105	28	-44	8	Hippocampus	-
	2	4.42	84	21	10	2	Putamen	-
	3	4.34	25	51	4	20	Inferior fronal	44
	4	4.22	26	20	-22	57	Precentral	4
	2	4.16	11	55	-8	-10	Superior temporal	22
	2	4.03	28	17	-38	26	Cingulate	31
	4	3.93	31	17	-91	32	Cuneus	19
	4	3.51	12	2	-26	16	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 5: Local maxima for LV4: regions that were predominantly related to cognitive reserve across task conditions

Hemisphere	Temporal lag	Bootstrap ratio	Spatial extent	Talairach coordinates			Gyral location	BA
				x	y	z		
Negative Saliences: Increased activity with reserve across task conditions								
Left								
	3	-4.53	21	-53	-16	-5	Superior temporal	22
Right								
	3	-5.58	90	9	-94	24	Cuneus	19
Positive Saliences: Decreased activity with reserve across task conditions								
Left								
	2	3.84	10	-46	8	26	Inferior/Middle frontal	9

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. Timeline of fMRI task procedure

Figure 2. Brain-behaviour correlation profiles and corresponding singular images for LV1 and LV2

a) LV1 brain-behaviour correlation profile separated by task. The correlation profile indicated that activity in negative salience brain regions correlated positively with age, and accuracy (ACC) during easy encoding events, and correlated positively with ACC during easy retrieval events. b) Singular image for LV1 showing negative voxel saliences (cool coloured regions). c) LV2 brain-behaviour correlation profile separated by task. The correlation profile indicated that activity in positive salience regions increased with age, and activity in negative salience regions decreased with age across tasks. ACC is short for accuracy. Error bars represent 95% confidence intervals. d) Singular image for LV2 of reserve B-PLS showing positive (warm coloured regions) and negative (cool coloured regions) voxel saliences. 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 ((2018)).

Figure 3. Brain-behaviour correlation profile and corresponding singular image for LV3 and LV4

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. Activity in negative salience regions increased with age at encoding and decreased with age at retrieval. ACC is short for accuracy. Error bars represent 95% confidence intervals. b) Singular 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, $p < 0.001$. c) LV4 brain-behaviour correlation profile separated by task. The correlation profile indicated that activity in negative salience regions increased with reserve across all task conditions (except for SH encoding), while activity in positive salience regions decreased with reserve across task conditions (except for SH encoding). ACC is short for accuracy. Error bars represent 95% confidence intervals. d) Singular 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.

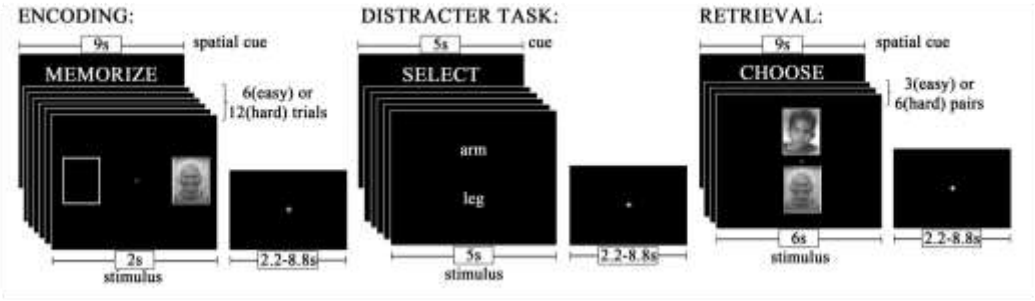
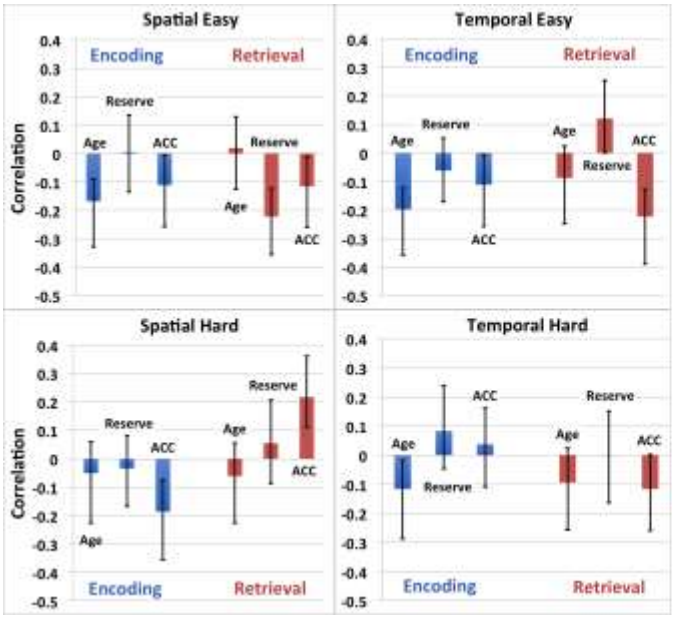
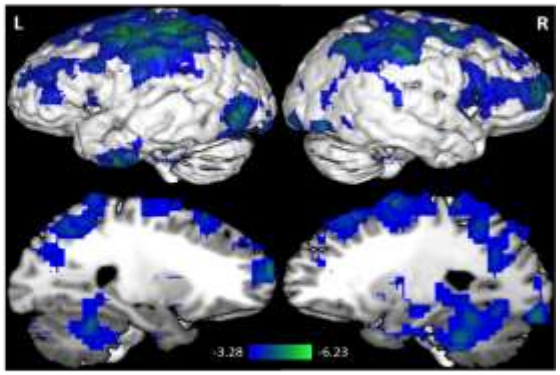

ENCODING:
9s
spatial cue
MEMORIZE
6(easy) or
12(hard) trials
2s
stimulus
2.2-8.8s
DISTRACTER TASK:
5s
cue
SELECT
arm
leg
5s
stimulus
2.2-8.8s
RETRIEVAL:
9s
spatial cue
CHOOSE
3(easy) or
6(hard) pairs
6s
stimulus
2.2-8.8s

Figure 2.

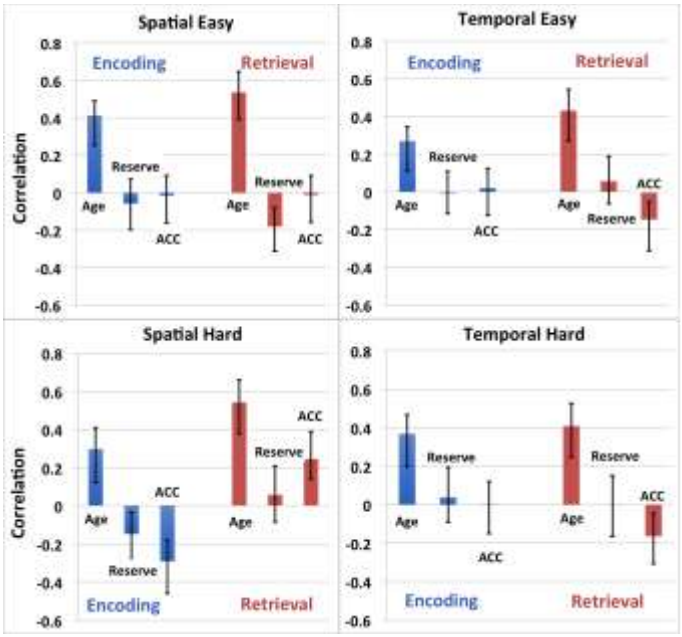
a)



b)



c)



d)

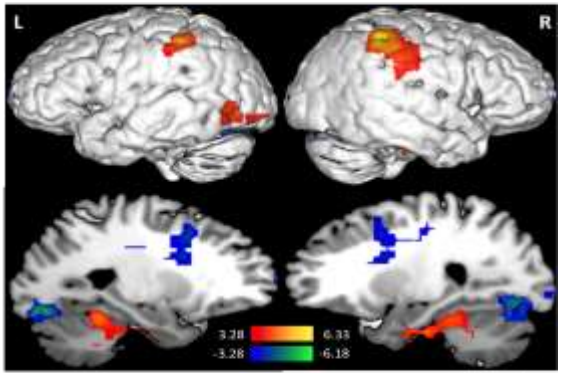
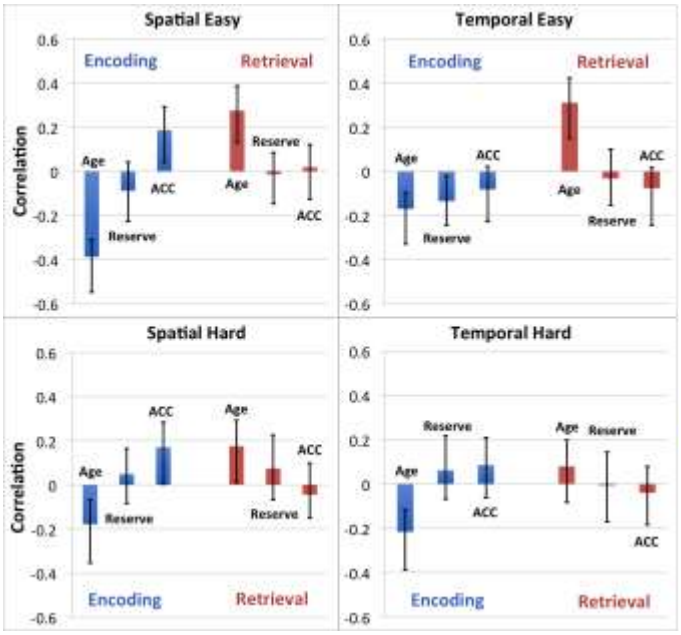
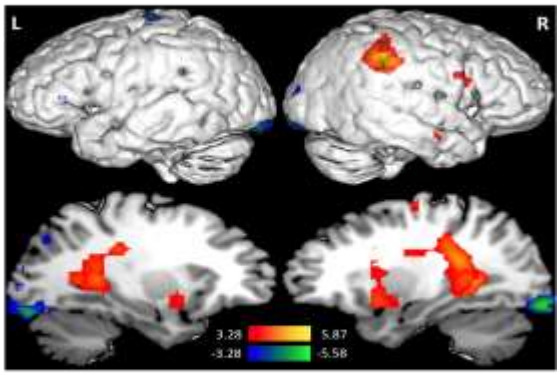


Figure 3.

a)



b)



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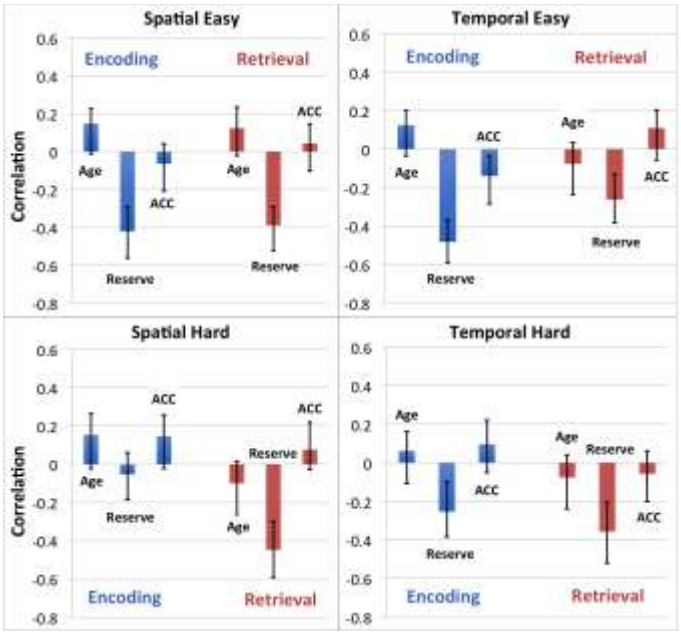

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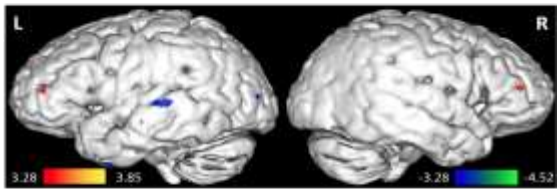

Supplementary material

Measurement of cortical thickness

CIVET is a processing pipeline consisting of various tools that allows for the automation and processing of a native MRI image in sequence (CBRAIN project, https://cbrain.mcgill.ca/). The pipeline starts with non-uniformity correction, by applying an N3 distance of 200 (Sled et al., 1998), tricubic interpolation, standardization to stereotaxic space (ICBM 152 dataset average brain in MNI space; Collins et al., 1994), brain masking, classification into 3 tissue classes (cerebral spinal fluid, grey-matter, and white matter), and surface extension. The inner and outer cortical surfaces were extracted using the Constrained Laplacian Anatomic Segmentation using Proximity (CLASP) algorithm (J. S. Kim et al., 2005; MacDonald et al., 2000). A 20 mm blurring kernel was used to spatial smooth the re-samples surfaces and the cortical thickness was measured using the t-link method (Lerch & Evans, 2005). Quality control was conducted to assess for precision of tissue classification and image registration using a cut-off of 15% tissue outside the skull mask. The script used to run CIVET for the current study is made publicly available (Rajah et al., 2020a).

Supplementary figure caption

Supplementary Figure 1. Visualized cortical thickness with t-statistical map (t-map) showing main effects of age and sex.
a) Brain areas demonstrating a main effect of age on cortical thickness with blue areas denoting thinner cortex with increased age. Light blue areas represent t-values surviving 1% False Discovery Rate (FDR) correction, while dark blue areas represent t-values surviving 5% FDR correction. b) Brain areas denoting differences in cortical thickness between males and females such that, blue areas represent regions were females had less cortical thickness than males and red areas represent brain regions were females had greater cortical thickness than males. Light blue areas and yellow areas represent t-values surviving 1% FDR correction, while dark blue areas and red areas represent t-values surviving 5% FDR correction. No effects of reserve were observed on cortical thickness in our sample.

Supplementary Figure 1.

a) b)