Individual differences in context memory performance and functional brain activity: The role of educational attainment and crystallized intelligence

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List of abbreviations

AD:	Alzheimer's disease
AET:	Attention at Encoding Task
AMNART:	American National Adult Reading Test
AP:	Anterior-posterior
B-PLS:	Behavioural partial least squares analysis
BA:	Brodmann area
BCST:	Berg Card Sorting Test
BDI-II:	Beck Depression Inventory
BOLD:	Blood-oxygen-level dependent
BOSS:	Bank of standardized stimuli
BSR:	Bootsrap ratio
CF:	Category fluency
CFQ:	Cognitive Failure Questionnaire
CIHR:	Canadian Institute of Health Sciences
CIVET:	Corticometric Iterative Vertex-based Estimation of Thickness
CLASP:	Constrained Laplacian Anatomic Segmentation using Proximity
CRUNCH:	Compensation-Related Utilization of Neural Circuits Hypothesis
CS:	Category switching
CVLT:	California Verbal learning Test
D-KEFS:	Delis-Kaplan Executive Function System
DCR:	Delay cued recall
DFR:	Delay free recall
DMN:	Default-mode network
DRG:	Delay recognition
DSSQ:	Dundee Stress State Questionnaire
EEG:	Electroencephalography
EDU:	Years of educational attainment
EPI:	Echo-planar imaging
FDR:	False discovery rate
fMRI:	Functional magnetic resonance imaging

FWHM:	Full-width at half maximum
GLM:	General linear model
HRF:	Hemodynamic response function
IQ:	Intelligence quotient
LF:	Letter fluency
LV:	Latent variable
MAAS-LO:	Mindful Attention Awareness Scale-lapses only
MCI:	Mild cognitive impairment
MMSE:	Folstein Mini-Mental State Examination
MNI:	Montreal Neurological Institute coordinate system
MTL:	Media temporal lobe
NART:	American National Adult Reading Test
NMI:	Normalized mutual information
NSERC:	Natural Science and Engineering Council of Canada
OA:	Older adults
PA:	Posterior-anterior
PCC:	Posterior cingulate cortex
PFC:	Prefrontal cortex
PHG:	Parahippocampal gyrus
PVT:	Psychomotor vigilance task
RM:	Repeated measures
ROI:	Region of interest
RT:	Response time
SART:	Sustained Attention to Response Task
SBREF:	Single-band reference image
SE:	Spatial easy
SH:	Spatial hard
SPM:	Statistical Parametric Mapping software
STAC:	Scaffolding Theory of Aging and Cognition
SVD:	Singular value decomposition
TE:	Temporal easy
TH:	Temporal hard
YA:	Younger adults

Abstract

The ability to remember spatial or temporal contextual features of past events (i.e., where or when a past experience has occurred) is an important component of episodic memory, and is an integral part of daily life. Although a multitude of factors can impact memory ability in healthy individuals, compromised attention at the time of memory formation, and advanced age appear to selectively hinder context memory. Yet, significant variability in memory function exists across individuals, and sociodemographic variables such as years of educational attainment and crystallized intelligence (IQ) have been proposed to partially mediate this variability. In this set of studies we aim to advance our knowledge by examining whether educational attainment and crystallized IQ can explain some of the inter-individual variance in the behavioural and neural effects pertaining to levels of attention at encoding and aging on context memory. We examine behavioural and neuroimaging data of healthy individuals who underwent functional Magnetic Resonance Imaging (fMRI) scanning while encoding and retrieving contextual memory details.

In study 1, we designed a novel and innovative event-related fMRI task paradigm to examine how the ebb and flow of attention during memory encoding influences the subsequent retrieval of associative context memory, and underlying brain activity in young adults. We demonstrate that variation in attention during encoding events predicts subsequent context memory performance. We also show that momentary interruption in attention at encoding is associated with enhanced activity in primary visual cortex and less deactivation of premotor/supplementary motor regions, which may be indicative of inefficient allocation of attentional resources towards associative encoding-related processes. Years of educational attainment and crystallized IQ did not account for inter-individual differences in these attentional effects on context memory performance or fMRI activity in this young adult sample. In study 2, we extend these findings by examining whether educational attainment and crystallized IQ can explain some of the inter-individual variability in the effects of aging on context memory performance, potentially via compensatory brain mechanisms that presumably attenuate the deleterious impact of brain aging. We examine this in a large cross-sectional adult lifespan sample spanning younger, middle-aged, and older adults and find that increased age was associated with enhanced anterior and lateral frontal, inferior parietal, occipito-temporal, and medial temporal activity at encoding, which may reflect age-related functional compensation. Yet, this compensatory pattern was not associated with years of educational attainment and crystallized IQ. Converging findings across both studies suggest that despite educational attainment and crystallized IQ being theoretically linked to individual differences in cognitive function across individuals, they are not sufficient to account for individual differences in the effects of attention at encoding or aging on context memory performance and underlying brain activity. These individual differences may be better explained by alternative factors that directly tap the neurocognitive processes of context memory task demands.

Résumé

La capacité à se souvenir des caractéristiques contextuelles spatiales ou temporelles d'événements passés (*c.-à-d.* où ou quand une expérience passée s'est produite) est une composante importante de la mémoire épisodique et fait partie intégrante de la vie quotidienne. Bien qu'une multitude de facteurs puissent avoir un impact sur la capacité de mémorisation chez les individus en bonne santé, une attention compromise au moment de la formation du souvenir et un âge avancé semblent entraver de manière sélective la mémoire contextuelle. Pourtant, la fonction de la mémoire varie considérablement d'un individu à l'autre, et il a été proposé que des variables sociodémographiques telles que le nombre d'années d'études et l'intelligence cristallisée (QI) servent de médiateur partiel à cette variabilité. Dans cette série d'études, nous visons à faire progresser nos connaissances en examinant si le niveau d'éducation et le QI cristallisé peuvent expliquer une partie de la variance interindividuelle concernant les effets comportementaux et neuraux relatifs aux niveaux d'attention à l'encodage et au vieillissement sur la mémoire contextuelle. Nous examinons les données comportementales et de neuro-imagerie recueillies auprès d'individus en bonne santé qui ont subi un examen d'imagerie par résonance magnétique fonctionnelle (IRMf) alors qu'ils encodaient et récupéraient des détails de mémoire contextuelle.

Dans le cadre de la première étude, nous avons conçu un paradigme novateur de tâche événementielle en IRMf pour examiner comment les fluctuations d'attention pendant l'encodage influencent la récupération ultérieure de la mémoire contextuelle associative et l'activité cérébrale sous-jacente chez les jeunes adultes. Nous démontrons que la fluctuation de l'attention pendant les événements d'encodage prédit la performance ultérieure de la mémoire contextuelle. Nous démontrons également que l'interruption momentanée de l'attention au moment de l'encodage est associée à une activité accrue dans le cortex visuel primaire et à une désactivation moindre des aires motrices supplémentaires et prémotrices, ce qui pourrait indiquer une allocation inefficace des ressources attentionnelles vers les processus associatifs liés à l'encodage. Les années de scolarité et le QI cristallisé n'expliquent pas les différences interindividuelles de ces effets attentionnels sur la performance de la mémoire contextuelle ou l'activité IRMf dans cet échantillon de jeunes adultes. Au cours de la deuxième étude, nous approfondissons ces résultats en examinant si le niveau d'instruction et le QI cristallisé peuvent expliquer une partie de la variabilité interindividuelle des effets du vieillissement sur la performance de la mémoire contextuelle, potentiellement par le biais de mécanismes cérébraux compensatoires qui atténuent vraisemblablement l'impact délétère du vieillissement cérébral. Nous examinons cette question dans un vaste échantillon transversal d'adultes de tous âges, et nous constatons que l'augmentation de l'âge est associée à une augmentation de l'activité frontale antérieure et latérale, pariétale inférieure, occipito-temporale et temporale médiane lors de l'encodage, ce qui pourrait refléter une compensation fonctionnelle liée à l'âge. Cependant, ce schéma compensatoire n'était pas associé aux années d'études et au QI cristallisé. Les résultats convergents des deux études suggèrent que, bien que le niveau d'instruction et le QI cristallisé soient théoriquement liés aux différences individuelles dans la fonction cognitive, ils ne suffisent pas à expliquer les différences individuelles quant aux effets de l'attention à l'encodage ou du vieillissement sur la performance de la mémoire contextuelle et l'activité cérébrale sous-jacente. Ces différences individuelles peuvent être mieux expliquées par des facteurs alternatifs qui exploitent directement les processus neurocognitifs des exigences de la tâche de mémoire contextuelle.

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Preface and Contribution of Authors

The elements of this thesis listed below constitute distinct and original contributions of knowledge in the domain of the cognitive neuroscience of episodic memory.

Elshiekh, A., Rajagopal, S., Parent, O., Chakravarty, M.M., & Rajah, M.N. (submitted). Variation in attention during memory encoding predicts subsequent associative context memory performance and modulates underlying fMRI activity

I formulated the primary research question for this study, designed the task paradigm, performed all the behavioural and neuroimaging data collection, had the idea for the analytical approach used in the study, and carried out data analysis, under Dr. Natasha Rajah's oversight and supervision. Sricharana Rajagopal and I shared the responsibility of preprocessing and management of neuroimaging data. Olivier Parent and Dr. Chakravarty assisted in aspects of neuroimaging data analysis. I had the primary responsibility of writing the manuscript, and Dr. Rajah supported the manuscript in an editorial capacity.

Elshiekh, A., Subramaniapillai, S., Rajagopal, S., Pasvanis, S., Ankudowich, E., & Rajah, M.N. (2020). The association between cognitive reserve and performance-related brain activity during episodic encoding and retrieval across the adult lifespan. Cortex, 129, 296-313.

This study was a follow-up to our previous lifespan study published in 2017 in a special issue of the journal *Cortex* on context memory. Dr. Natasha Rajah designed and funded the initial lifespan study. Stamatoula Pasvanis, Elizabeth Ankudowich, and Sricharana Rajagopal performed additional data collection and neuroimaging data processing. I spearheaded conceptualization and formulation of analytical approach used in the study and carried out data analysis under Dr. Rajah’s mentorship. Sivaniya Subramaniapillai assisted with interpretation of neuroimaging findings. I had the primary responsibility of writing the initial manuscript, and Dr. Rajah and I both contributed to subsequent revisions.

Chapter 1. Introduction

The ability to travel back in time is a topic that has long been embraced by science fiction and is often regarded as merely wishful thinking that belongs to children's fantasy books. Unbeknownst to us, we often travel back into our past on a daily basis, albeit not in the physical but in the mental sense, to re-experience past episodes of our lives. This ability has been coined episodic memory in 1972 by Endel Tulving, which he rightfully described as a true marvel of nature. Tulving proposed that episodic memories are autobiographical in nature (e.g., the last time I visited Egypt), and are qualitatively different than semantic memories, which reflect a person's general knowledge (e.g., The Nile River flows through Egypt). He elaborated on this distinction by saying:

> Episodic memory receives and stores information about temporally dated episodes or events, and temporal-spatial relations among these events. A perceptual event can be stored in the episodic system solely in terms of its perceptible properties or attributes, and it is always stored in terms of its autobiographical reference to the already existing contents of the episodic memory store . . . Sematic memory is the memory necessary for the use of language. It is a mental thesaurus, organized knowledge a person possesses about words and other verbal symbols (Tulving, 1972, pp. 385-386).

Episodic and semantic memory systems are not entirely separable, and may overlap to a certain extent (see Squire, 1987, for a discussion). One major distinction between both systems is that, while semantic memory tends to reflect facts, ideas, and concepts acquired over time that are free of contextual details, episodic memory system contains information about specific event elements (item memory) that are tied to the situational context in which they occurred (source/context memory) (Tulving, 2002). Item memory refers to memory for the content of a given event, while source/context memory contains information about when, where, and how an individual experienced the event. This terminology was made popular by Marcia Johnson and colleagues in the early 1990s when they introduced the Source Monitoring framework (Johnson et al., 1993). According to this framework, episodic memories are not singular, but contain records of perceptual, spatial, temporal, and affective features, as well as the cognitive operations involved at the time of memory formation or encoding. When these contextual features are bound together with the focal element ("the item") of an event, the event becomes differentiated from other past experiences and is more likely to be retrieved as a distinct memory episode. In particular, the spatial and temporal context in which an event occurred is considered a defining feature of episodic memory, and it is the association or binding between the central item in an event and these spatio-temporal features that gives a memory its episodic nature (Tulving, 1972, 2002).

The advent of neuroimaging over the last few decades including functional Magnetic Resonance Imaging (fMRI) has revolutionized the field of cognitive neuroscience, and has afforded memory researchers a unique opportunity to investigate the neural correlates of episodic memory, including how the brain encodes and retrieves context information. A key feature of fMRI is that it allows for examining event-related, task-specific blood-oxygen-level dependent (BOLD) activity in the brain with a reasonable degree of spatial specificity in a non-invasive fashion. BOLD activity reflects regional differences in the ratio of oxygenated to deoxygenated blood. Neural activity alters this ratio by influencing cerebral blood flow, cerebral blood volume, and cerebral blood oxygen consumption. Therefore, the BOLD signal is an indirect measure of neural activity (D'Esposito et al., 2003). While many questions pertaining to context memory remain unanswered, a substantial amount of BOLD fMRI studies have been conducted to uncover the neural mechanisms associated with encoding and retrieving contextual memory details.

1.1 Brain and cognitive mechanisms implicated in context memory

There is a growing body of neuroimaging work concerning the neural correlates of encoding and retrieving contextual information associated with events. Typically, these studies examine spatial or temporal context memory by presenting participants lying in an fMRI scanner a set of stimuli on a computer display during an encoding phase, and then asking them to explicitly remember either the spatial location (Burgess et al., 2001; Cansino et al., 2002, 2015; Rugg et al., 1999; Slotnick et al., 2003) or the temporal order (Eyler Zorrilla et al., 1996; Jenkins & Ranganath, 2010, 2016; Konishi et al., 2002; Rajah et al., 2008; Rajah & McIntosh, 2006; St. Jacques et al., 2008; Suzuki, 2002; Tubridy & Davachi, 2011) of the stimuli respectively at a later retrieval phase. Some studies also examine spatial and temporal context memory within the same paradigm (e.g., Hayes et al., 2004; Kwon et al., 2016; Rajah et al., 2010). Broadly speaking, successful context memory relies on activation of regions related to stimulus perception (i.e., ventral occipito-temporal regions for visual stimuli), prefrontal cortex (PFC), the hippocampus and surrounding medial temporal lobe (MTL) regions, and parietal cortical regions.

Encoding and retrieving contextual details are fundamentally reliant on our ability to perceive (i.e., identify, become aware of) external information, and our ability to engage in reflective processing (e.g., evaluation and organization) of internal mental representations. In theory, these capacities are subserved by strategic cognitive operations (i.e., cognitive control processes), which allow for flexible, goal-directed thought. The lateral PFC is thought to play a key role in supporting the kind of control operations that allows for the selection, elaboration, and organization of goal-relevant information at encoding. At retrieval, the lateral PFC may be involved in controlled monitoring and evaluation of active mental representations. Specific subregions within the PFC may mediate these strategic processes involved in context memory (see Mitchell & Johnson, 2009; Rajah & D'Esposito, 2005; Ranganath & Blumenfeld, 2008, for reviews).

PFC control regions do not work in isolation, but operate in conjunction with other areas such as posterior sensory regions to support context memory. Successful context memory hinges on what specific perceptual features of an experience are encoded, and how well those features are bound together into initial representations. Therefore, perceptual processing in category-specific areas of posterior sensory cortices plays an important role in context memory. Furthermore, there is evidence suggesting that PFC control regions bias the sensory cortices to only select and process a relevant subset of incoming information. This top-down modulation or biasing of the sensory cortices by PFC regions, allows for promoting high fidelity perceptual representations for downstream processing in the hippocampus and surrounding MTL regions (Summerfield et al., 2006; Uncapher et al., 2011). The binding of those perceptual representations into a single, highly contextualized event is thought to take place in the MTL (see Eichenbaum et al., 2012; Rudy, 2009 for reviews). The exact contribution of the hippocampus and surrounding MTL regions to the binding processes and construction of a cohesive mental representation remains a topic of debate (e.g., Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2012; Olsen et al., 2012; Sheldon & Levine, 2016). Yet, the interplay between PFC control regions and the MTL may also influence successful subsequent remembering (Anderson & Huddleston, 2012; Ankudowich et al., 2019; Ranganath et al., 2005; Simons & Spiers, 2003).

In addition to PFC, posterior sensory, and MTL regions, the parietal cortex also plays an important role in representing, or directing attention to reflective processing of context features that give memories their episodic character. There is evidence suggesting that inferior areas of the parietal cortex may contribute to the phenomenological experience of remembering rich contextual details (Wagner et al., 2005). In an attempt to delineate parietal contributions to memory, two conceptually similar hypotheses that follow directly from Corbetta and Shulman's (2002) account of a dual attentional system in the parietal cortex were proposed (Cabeza et al., 2008; Ciaramelli et al., 2008). These hypotheses suggest that more superior posterior parietal regions are involved in goal-driven, top-down allocation of attentional resources towards internally generated mnemonic representations, while more inferior posterior parietal regions are involved in stimulus-driven, bottom up capture of attention by salient features that may be perceived or retrieved (Cabeza et al., 2008; Ciaramelli et al., 2008). More recent evidence suggests that some lateral parietal areas, especially the angular gyrus may integrate information across multiple domains and modalities, and hence support the representation of event-specific information (Bonnici et al., 2016; Wagner et al., 2015). Activity in angular gyrus may also be associated with the subjective experience of vivid remembering (Kuhl & Chun, 2014). Therefore, the parietal cortex may support context memory by attending to/monitoring internal mnemonic representations, selecting relevant active information that may be perceived or retrieved, and facilitating the integration of information across various domains.

In summary, cognitive operations in the PFC, posterior sensory cortices, MTL, and the parietal cortex are instrumental in creating a vivid and contextualized recollective experience. These operations mediate our ability to selectively perceive relevant information that is consistent with goal-driven agendas, the ability to reflectively process represented information, and the ability to integrate features into coherent representations. Disruption of these processes during encoding or retrieval may compromise memory for context.

1.2 Factors impacting context memory in healthy individuals

Inability to remember contextual details of past events may be mildly disconcerting. For example we may spend a few extra minutes around a parking lot to try and remember where we parked our car. However, it may also have dire consequences such as in cases of eyewitness testimony. In severe cases where brain damage has occurred (e.g., Henry Molaison who had bilateral MTL resection; Scoville & Milner, 1957), context memory deficits may be profoundly disruptive. Failure to remember contextual details is also a salient feature of Alzheimer's disease (El Haj & Antoine, 2018; McKhann et al., 2011).

Since context memory is the product of perceptual and reflective processes engaged during encoding and retrieval, anything that disrupts these processes and prevents information from becoming fully contextualized will impair context memory even in healthy individuals. For example, time pressure (Benjamin & Craik, 2001), acute stress (Hidalgo et al., 2019; Schwabe et al., 2009), and sleep deprivation (Cousins & Fernández, 2019; Harrison & Horne, 2000) impair context memory. However, these factors seem to have a global effect on cognitive function and are not restricted to context memory (Cousins & Fernández, 2019; Killgore, 2010; Sandi, 2013; Schoofs et al., 2009). On the other hand, encoding under divided attention conditions disproportionately impairs context memory compared to item memory (Troyer et al., 1999; Troyer & Craik, 2000). In addition, healthy older adults exhibit disproportionate deficits in context memory relative to item memory (Spencer & Raz, 1995). In the following section we discuss the effects of attention during encoding and aging on context memory in more detail.

1.2.1 Effects of attention at encoding on context memory

In order to understand how attention during encoding impacts context memory, it is necessary to first consider how investigators conceptualize attention. As a concept, attention lacks a clear definition, and is still being debated in the literature (e.g., Di Lollo, 2018; Hommel et al., 2019; Lindsay, 2020). Despite its several and vague definitions, at its core, attention reflects the flexible allocation of limited computational/processing resources towards a task or multiple tasks (Lindsay, 2020; Parasuraman, 2000). In fact, some researchers argue that memory processes are acts of attention. While memory encoding involves selective attention to external stimuli (perceptual attention), retrieval involves attention to internal mental representations (reflective attention) (Chun & Johnson, 2011). This perspective highlights the complexity and interrelatedness of attention and memory systems.

Much of the work that has examined whether and how attention impacts episodic memory has used dual-task, divided attention paradigms (e.g., encoding stimuli while simultaneously monitoring auditory tones) (Anderson et al., 1998; Craik et al., 1996; Craik et al., 2018; Kensinger et al., 2003; Naveh-Benjamin et al., 1998; Park et al., 1989). Relative to encoding under full attention conditions, episodic memory performance is impaired under divided attention, and memory costs are greater for context memory compared to item memory (Troyer et al., 1999; Troyer & Craik, 2000). In contrast, retrieval is relatively immune to the effects of divided attention as memory performance is spared when attention is divided at test (Anderson et al., 1998; Craik et al., 1996; Naveh-Benjamin et al., 2006). These findings imply that encoding operations are especially demanding of attentional resources, while retrieval may be characterized by some degree of automaticity (Baddeley et al., 1984; Craik et al., 1996; Mulligan & Picklesimer, 2016; Naveh-Benjamin et al., 2000). More critically, investigators suggest that encoding contextual details is more effortful and taps attentional resources to a larger extent than item memory (Troyer et al., 1999; Troyer & Craik, 2000). In an effort to delineate the encoding processing mechanisms that are compromised in the face of competing attention, Naveh-Benjamin and colleagues (2014) argued that dividing attention not only impairs effortful and strategic encoding operations (i.e., reflective processing), but also impairs more automatic processes (e.g., stimulus registration). This conclusion is based on the fact that divided attention costs on memory performance is equivalent whether encoding is intentional or incidental.

A consistent finding across many divided attention studies is that encoding-related activity in frontal control regions, particularly the lateral PFC, as well activity in MTL regions are attenuated when a challenging secondary task is simultaneously performed. Parietal regions are also modulated by divided attention paradigms possibly reflecting their role in directing attention in conjunction with the PFC (Anderson et al., 2000; Fletcher et al., 1995; Kensinger et al., 2003; Shallice et al., 1994; Uncapher & Rugg, 2005). Overall, these findings suggest that encoding processes mediated by the lateral PFC and parietal cortex rely on general attentional mechanisms, which are taxed when attention is divided. Subsequently, this may result in reduced or inefficient biasing of the sensory cortices, which ultimately leads to lower fidelity perceptual representations being fed forward to higher order brain regions such as the MTL for further processing, thereby compromising subsequent memory (Uncapher & Rugg, 2009). Indeed, there is evidence suggesting that attention modulates activity in posterior sensory cortices (Gilbert & Li, 2013; Maunsell & Treue, 2006), and medial temporal lobe areas that provides input to the hippocampus (Aly & Turk-Browne, 2016).

Investigators have also examined how moment-by-moment variations in attention at encoding (as indexed by variations in response time measures) impacts episodic remembering (deBettencourt et al., 2018; Smallwood et al., 2006). The literature on this topic is scarce, but such work is insightful since our attention naturally ebbs and flows even in the absence of explicit attention manipulations (Esterman et al., 2013, 2014), which may impact subsequent episodic remembering (Markant et al., 2014). Indeed, deBettencourt and colleagues (2018) demonstrated that item memory performance was impaired when participants' attention during encoding was in a compromised state as indexed by variations in response time. Furthermore, neuroimaging evidence suggests that the rate of successful memory encoding varies over time in part due to fluctuations in the neural signals underpinning an individual's current level of attention (Fernandez et al., 1999; Otten et al., 2006; Turk-Browne et al., 2006; Yoo et al., 2012). To my knowledge, there are no studies that have investigated the behavioural effects and underlying brain mechanisms associated with moment-by-moment variations in attention at encoding as they relate to memory for contextual details and as such, these effects remain largely unknown.

1.2.2 Effects of advanced age on context memory

Previous aging studies have demonstrated that relative to younger adults, older adults tend to show memory deficits, especially for context compared to item memory (see Old & Naveh-Benjamin, 2008; Spencer & Raz, 1995 for reviews). This may in part reflect age-related differences in strategic and associative processing at encoding and retrieval (Shing et al., 2010; Spaniol, 2015). Moreover, neuroimaging studies investigating context memory have revealed age-related functional changes in PFC, posterior sensory cortices, MTL, and parietal cortex during both encoding and retrieval (Ankudowich et al., 2016; Dennis et al., 2008; McDonough et al., 2013; Mitchell et al., 2000, 2013), which may underlie the observed behavioural deficits in context memory with advanced age.

Compared to younger adults, older adults show structural and functional changes in the lateral PFC (Glisky et al., 2001; Mitchell & Johnson, 2009; Rajah & D'Esposito, 2005), which may impede the control operations mediated by PFC regions that are required for successful context memory encoding. For instance, age-related changes in PFC function may lead to difficulties in suppressing/or inhibiting task-unrelated information with advanced age (Desimone, 1998; Hasher & Zacks, 1988; Miller & Cohen, 2001), thereby impairing the ability to selectively encode relevant perceptual features (Gazzaley et al., 2005). Additionally, relative to younger adults, older adults show attenuations in hippocampal activity during associative encoding, as well as attenuations in category-specific regions of the visual cortex relative to younger adults (Dennis et al., 2008). The activation patterns supporting visuoperceptual processing in these category-specific regions of the visual cortex also become less selective/distinct (i.e., dedifferentiated) with advanced age (Bowman et al., 2019; Koen et al., 2020; Park et al., 2004; Voss et al., 2008). Overall, these findings demonstrate how age-related brain changes may interfere with the encoding operations that support successful context memory performance. However, functional brain changes with advanced age also impact how well cohesive memory representations are revived and evaluated at retrieval.

Age-related functional changes in the lateral PFC and parietal regions are associated with differences in the ability to reflectively evaluate/monitor retrieved information (Daselaar et al., 2005; McDonough et al., 2013; Morcom et al., 2007). For example, older adults are more susceptible to task interference effects at retrieval (Jacoby et al., 2005), and may have difficulty in selecting relevant memory representations, while simultaneously gating out irrelevant information that is inconsistent with task goals (Raye et al., 2008). In addition to deficits in monitoring active memory representations at retrieval, older adults may also have difficulty in accessing bound components such as item-context associations (associative deficit hypothesis: Naveh-Benjamin, 2000). Age-related changes in PFC and MTL regions have both been suggested to play a role in the associative deficit observed in older adults (Dennis et al., 2008; Naveh-Benjamin, 2015). Taken together, findings across studies suggest that age-related brain changes are associated with deficits in associative and strategic processes at encoding and retrieval that may contribute to poorer context memory with advanced age.

As discussed above, neuroimaging studies of age-related changes in context memory often report attenuations in neural activity in older adults compared to younger adults (e.g., Dennis et al., 2008). However, increased activity in other brain regions with age may also be observed along with these age-related reductions (Cabeza et al., 2002). Under-recruitment of brain regions related to context memory in older vs. younger adults is often interpreted as a reflection of age-related functional deficits. Yet, there is less consensus regarding the functional significance of age-related over-recruitment of brain regions (Maillet & Rajah, 2014; Morcom & Henson, 2018; Rajah & D'Esposito, 2005). On the one hand, increased activity with age may reflect less efficient or less specific neural recruitment owing to a dedifferentiation of brain function accompanying age (Park et al., 2001; Park et al., 2004). On the other hand, it may reflect a compensatory mechanism that contributes to maintenance of task-performance in response to age-related deficits elsewhere in the brain (Cabeza et al., 2002; Reuter-Lorenz & Cappell, 2008). To assess whether additional recruitment with age represents compensation or dedifferentiation, increased activity must be examined in relation to task performance (Cabeza et al., 2018; Grady, 2008). For example, additional recruitment with age that is also associated with better context memory performance can be considered compensatory (Cabeza & Dennis, 2013). Nonetheless, there is significant variability in episodic memory function (e.g., Christensen et al., 1999; Wilson et al., 2002), and further study is required to elucidate some of the factors that may contribute to individual differences in the utilization of compensatory mechanisms to support context memory with advanced age.

1.2.3 Educational attainment and crystallized intelligence as mediators of individual differences in context memory

The majority of studies discussed above considered the mean effect on context memory performance and underlying neural activity as a factor of attention during encoding or advanced age. Yet, significant variability in episodic memory function exists across the adult life span (see Tucker-Drob & Salthouse, 2011 for a review). This raises the possibility that certain factors may moderate (i.e., influence) the relationship between attention during encoding and increased age on context memory, giving rise to individual differences. With regards to aging, a myriad of demographic factors such as sex/gender, race/ethnicity, occupation, as well as genetic risk factors, and biological factors such as cardiovascular health impact episodic memory (Early et al., 2013; Foubert-Samier et al., 2012; Lundervold et al., 2014; Small et al., 2004; Song et al., 2020). Not to mention factors related to unhealthy behaviours (e.g., smoking), chronic health conditions, nutrition, and pharmaceuticals that may also impact episodic memory function (e.g., Ahn et al., 2021; Cansino et al., 2021; Evans et al., 2019; Papenberg et al., 2017). Individual differences in these factors may therefore contribute to individual differences in context memory in aging.

One of the most influential theories that attempt to explain age-related individual differences in memory and cognition more broadly is the *cognitive reserve* theory (Stern, 2002; Stern et al., 2018). The concept centers around how individual differences in the processing of cognitive tasks shapes individuals' susceptibility to the adverse effects of age-related brain changes on cognitive function. These individual differences in task processing a) result from years of educational attainment and crystallized intelligence (among other factors) and b) mediate (i.e., explain) individual differences in episodic memory function in aging. For example, there is cross-sectional and longitudinal evidence suggesting that individuals who are more educated, exhibit relatively modest declines in episodic memory function with age compared to those who are less educated (Angel et al., 2010; Anstey & Christensen, 2000; Cullum et al., 2000; Lachman et al., 2010; but see Lövdén et al., 2020). Several neural mechanisms of cognitive reserve have been hypothesized. Those with higher levels of cognitive reserve (i.e., more years of education and crystallized IQ) may either a) show less recruitment of task related brain regions to perform a given task without compromising performance (i.e., neural efficiency); b) maximize recruitment of task-related brain regions under increasing demands (i.e., neural capacity); or c) utilize alternate networks to maintain or improve performance (i.e., neural flexibility) (Barulli & Stern, 2013). The ability of some older adults to compensate for age-related decline by engaging alternate neural networks may therefore be thought of as enhanced neural flexibility. In fact, Barulli and Stern (2013) argue that functional compensation is a mechanism of cognitive reserve, and thus is dependent on it (but see Cabeza & Dennis, 2013 for an alternate discussion). Yet, it remains unclear whether higher levels of education and crystallized IQ directly benefit context memory performance with increased age through compensatory neural mechanisms.

It is important to note that cognitive reserve is a hypothetical construct, and there currently exists no measure of cognitive reserve with undisputed construct validity (Jones et al., 2011; Nilsson & Lövdén, 2018). Nonetheless, years of educational attainment and levels of crystallized intelligence, which are tightly linked to one another, have often been used to estimate cognitive reserve (Stern et al., 2018). This likely stems from the assumption that years of education contributes to the accumulation of knowledge and cognitive skills (e.g., cognitive strategies) that allows individuals to process tasks in ways that render them less susceptible to the deleterious effects of age-related brain changes (Tucker & Stern, 2011). In that sense, cognitive reserve implies the existence of crystallized abilities that can lessen the impact of brain aging on cognitive function. In addition, years of education and levels of crystallized intelligence likely reflect a broad constellation of lifestyle and socio-contextual opportunities. For example, parents with higher income and education may influence their children's access to education and may provide greater social, financial, and health resources that affect development (Davis-Kean, 2005; Hill & Tyson, 2009). Individuals with higher education are also more likely to have many favourable life conditions (e.g., higher occupational attainment, participating in leisure activities, reduced health risk behaviours), which contribute to cognitive reserve (Stern et al., 2018). Clearly, the concept of cognitive reserve is broad and complex, but focusing on measures of education and crystallized intelligence may provide some insight on the factors that may influence individual variability in context memory.

The bulk of the studies looking at the association between measures of educational attainment and crystallized abilities in relation to episodic memory have done so within the framework of aging and cognitive reserve. This is likely due to the potential protective role that these factors can play in softening the impact of age-related changes on episodic memory. Some researchers acknowledge that it is difficult to assess associations between these factors and episodic memory in younger individuals who have yet to obtain additional benefits in their working years that contribute to their "reserve" (e.g., Opdebeeck et al., 2016). However, others argue that although additional cognitive reserve can be accrued in middle- and old-age, most reserve accumulates during childhood, and young adulthood (Cabeza et al., 2018). The latter view is inline with the fact that educational attainment and crystallized abilities are mostly established by young adulthood, and associations between education and cognitive function are observed in all stages of the adult lifespan (Lövdén et al., 2020). Therefore, regardless of how education and crystallized intelligence may lessen the impact of age-related brain changes on episodic memory, these factors may also contribute to individual differences in context memory in younger adults by influencing the relationship between attention at encoding and context memory. This has not yet been tested to my knowledge, and if present, the neural mechanisms underlying that relationship remain unknown.

1.3 Overview and rationale

The ability to remember contextual details of past events is crucial to our daily functioning. There are a multitude of factors that can impact context memory, but some of the most studied factors in healthy adults include levels of attention at encoding, and advanced age. In more recent years, memory researchers have started to shift from simply studying population level phenomenon to addressing individual differences, but questions regarding the factors that mediate these differences and the neurocognitive mechanisms involved remain. Educational attainment and crystallized IQ represent a broad set of lifestyle and environmental opportunities that contribute to the flexible use of cognitive strategies to encode and retrieve information, and hence make for good candidates in studying individual differences in context memory. The overarching objective of the following studies is to investigate whether educational attainment and crystallized IQ can explain some of the inter-individual variance in the behavioural and neural effects of levels of attention at encoding and aging on context memory.

Study 1. Previous studies investigating the link between attention at encoding and context memory have utilized dual-task, divided attention paradigms. However, emerging evidence suggest that levels of attention naturally ebb and flow while encoding information, which may impact the subsequent mnemonic fate of stimuli. Examining the association between this variation in levels of attention at encoding and context memory is important for informing theories of episodic memory. Furthermore, current task paradigms examining how variations in attention at encoding impact subsequent memory (e.g., deBettencourt et al., 2018; Smallwood et al., 2006) are potentially susceptible to the effects of speed-accuracy tradeoffs (Helton, 2009; Seli et al., 2013), and thus, a new task paradigm is warranted. The primary aim of study 1 was to examine how variations in levels of attention at encoding may impact the subsequent retrieval of items and their contextual details, and underlying brain activity using a novel and innovative event-related fMRI task in a sample of young adults. A secondary aim of study 1 was to examine whether education and crystallized IQ can explain some of the inter-individual variance in the effects of attention on memory performance and fMRI activity.

Study 2. While context memory is also impacted by advanced age, tremendous inter-individual variability exists in episodic memory with age, and some older adults show equivalent performance to their younger counterparts (Tucker-Drob & Salthouse, 2011). Years of education and crystallized IQ have been proposed as mediators of inter-individual variability in episodic memory aging, potentially via compensatory brain mechanisms that attenuate the deleterious impact of brain aging in those who are more educated and have higher crystallized IQ (Stern, 2009). The primary aim of Study 2 was to investigate whether higher levels of education and crystallized IQ were related to better task-fMRI context memory performance, and functional compensatory activity patterns in the aging brain. We examined whole-brain activity patterns in a large cross-sectional adult lifespan sample spanning younger, middle-aged, and older adults who underwent fMRI scanning while encoding and retrieving contextual memory details.

Chapter 2. Study 1: Variation in attention during memory encoding predicts subsequent associative context memory performance and modulates underlying fMRI activity

Article submitted

2.1 Abstract

The ebb and flow of one's attention affects episodic memory encoding success. Emerging evidence suggests that variation in pre-stimulus attention and/or attention during encoding events impact subsequent memory performance for item memory. It remains unclear how this attention variability may impact the subsequent retrieval of items + their contextual details (associative context memory) and underlying brain activity at encoding. Thirty young adults participated in an event-related fMRI task. On each trial, they had to respond as quickly as possible to a central fixation cross that expanded in size after a random duration. They then had to encode a picture of an object and its spatial location. Memory for the object-location associations was tested during retrieval. Response time (RT) to the fixation cross presented prior to each object gauged pre-stimulus attention levels on a trial-by-trial basis, while RT to the fixation cross that ensued each object indexed the state of attention during the encoding events. Relatively longer RTs on a trial-by-trial basis indicated a brief interruption in attention. The behavioural findings revealed that the state of attention during encoding events (but not pre-stimulus attentional state) predicted subsequent associative context memory performance. To explore this attentional effect on encoding-related brain activity, we entered trial-by-trial pre-stimulus RT and post-stimulus RT as parametric modulators in an fMRI GLM model. We found that post-stimulus RT (but not pre-stimulus RT) modulated encoding-related activity. Momentary interruptions in attention at

encoding were associated with enhanced activity in primary visual cortex and less deactivation of premotor/supplementary motor regions, which may be indicative of inefficient allocation of attentional resources towards associative encoding-related processes.

2.2. Introduction

Episodic memory is the ability to encode, store, and retrieve past experiences in rich contextual detail (Tulving, 2002). Successful episodic memory encoding is dependent on one's level of attention (Chun & Turk-Browne, 2007; Craik et al., 1996). Indeed, moment-by-moment variations in attention at encoding have been linked to memory performance. For example, subsequent memory performance for an item was predicted by a response time (RT) index of attention, and memory performance was better on trials where pre-stimulus attention levels were relatively high (deBettencourt et al., 2018).

In general, attention and memory are intricately related (see Hannula, 2018), and the relationship between attention and memory has primarily been studied by examining how divided attention at encoding impacts subsequent memory performance (Craik et al., 1996; Naveh-Benjamin et al., 1998). Other studies investigating how attention impacts episodic memory encoding have utilized intermittent thought probes that explicitly evaluate whether participants' attention was externally directed on the encoding task, or whether they were experiencing task-unrelated thoughts (TUT) (e.g., Maillet & Rajah, 2014; Smallwood et al., 2006). These studies demonstrate that TUT at encoding are associated with lower memory accuracy implying that the ebb and flow of attention at encoding impacts subsequent memory. Yet, trial-by-trial variations in attention and their relationship to successful memory encoding have been less studied. In the present study, we utilize an RT measure of attention on a trial-by-trial basis to investigate whether variation in attentional state preceding and/or during an episodic event to be encoded, predicts whether it would be recalled along with its contextual details. We also explore the neural underpinnings of this attentional variation at encoding using functional magnetic resonance imaging (fMRI).

As mentioned above, previous behavioural studies investigating the role of attention on episodic memory encoding have mostly relied on dual-task or divided attention paradigms (Anderson et al., 1998; Craik et al., 1996; 2018; Naveh-Benjamin et al., 1998; Troyer et al., 1999; Troyer & Craik, 2000). These paradigms investigate the stages of memory processing most prone to disruption in the face of distraction, and therefore those that are most in need of attentional resources under normal conditions (Hannula, 2018). In divided attention paradigms, participants are asked to encode a list of words while simultaneously engaging in a secondary task (e.g., monitoring certain tones) (Anderson et al., 1998; Kensinger et al., 2003; Park et al., 1989). Relative to encoding under full attention conditions, dividing attention at encoding impairs free recall, cued recall, and recognition memory performance (Anderson et al., 1998; Baddeley et al., 1984; Craik et al., 1996, 2018; Fernandes & Moscovitch, 2000; Naveh-Benjamin & Guez, 2000). Moreover, memory performance costs under divided attention are greater for contextual memory details compared to item memory, especially when spatial location is used as the context memory task (Troyer et al., 1999; Troyer & Craik, 2000). In contrast, dividing attention at retrieval has minimal effects on memory performance (Craik et al., 1996; Naveh-Benjamin et al., 1998; Naveh-Benjamin et al., 2006). These results have been interpreted to suggest that memory encoding operations are especially demanding of attentional resources. Yet, fewer studies have investigated the behavioural markers of spontaneous drifts of attention prior to (pre-stimulus attention) or during stimulus presentation in relation to episodic memory formation.

Researchers have typically used variations of the sustained attention to response task (SART; Robertson et al., 1997) to investigate how variability in the state of attention affect memory encoding. Traditional SART requires participants to press a button in response to a frequent non-target (GO) stimulus, and withhold button pressing when a non-frequent target (NOGO) stimulus appears on the screen. Failure to suppress responses to NOGO stimuli has been used to index attention failures. A hallmark feature of the SART is an acceleration of RT to the NOGO stimulus preceding an error, followed by a deceleration of RT to the GO stimulus following an error. This variation in RT arguably reflects the disengagement of attention from task-relevant information, and re-direction of attentional resources to the task at hand respectively (Manly et al., 1999; Robertson et al., 1997). One study adapted the SART to investigate how variation in attention during encoding impacted verbal memory performance (Smallwood et al., 2006). In this study, participants were shown a sequence of frequent non-target words (GO) for which they were asked to respond to, and non-frequent target words (NOGO) for which they were asked to withhold response. Participants were either assigned to an incidental or intentional encoding condition for the words presented. Retrieval performance was measured via cued recall and results were analysed by a process dissociation method (Jacoby, 1998) to distinguish whether words were retrieved based on recollection or familiarity. Regardless of group assignment, participants showed no difference in probability of recollection- or familiarity-based recall prior to an error (i.e., responding to a NOGO stimulus). However, they were more likely to retrieve words based on recollection after an error has been made, presumably reflecting re-direction of attention at encoding to task-relevant information, thereby increasing chances of recollection-based recall (Smallwood et al., 2006). Another study examined the effect of spontaneous drifts in levels of attention on incidental encoding performance (deBettencourt et al., 2018). Participants were shown a series of images sequentially without delay, each for 1 sec. For each image, they were asked to make a categorical decision as fast as possible via button pressing to indicate whether the image reflects an indoor or an outdoor scene. The task was designed so that 90% of the images came from one category (e.g., outdoor), and 10% came from the other category, thereby ensuring that the task was repetitive in nature. Similar to a typical SART task, participants may get accustomed to responding to the frequent GO stimulus (i.e., outdoor) when attention had presumably been disengaged from the task as reflected by relatively quicker RTs, and therefore may be more likely to commit an error of commission (i.e., pressing outdoor for an indoor stimulus). In contrast, it was predicted that when participants' attention was directed on the task, they would be less likely to exhibit faster RTs and less likely to commit errors on the task. Indeed, the results confirmed these predictions. More importantly, when retrieval performance for the infrequent NOGO stimuli was assessed the stimuli were more likely to be forgotten if the average RT of the preceding three stimuli was relatively quick, presumably reflecting a pre-stimulus interruption in attention. Based on these results, the authors created a real-time adaptive task to systematically present stimuli from the infrequent category when the attention state of the participant may have dipped below a certain threshold. This threshold was based on a running RT average of the three stimuli preceding a certain stimulus. Results were replicated, and memory for the non-frequent stimuli was worse when participants' pre-stimulus attention was in a compromised state (deBettencourt et al., 2018).

Results from studies discussed above that combined SART with traditional memory paradigms, support the idea that the ebb and flow of attention at encoding can influence item memory accuracy even before the items are presented. Yet, it remains unclear how pre-stimulus attention variation at encoding may impact associative context memory performance. Since encoding contextual details related to an item is more effortful and requires greater attentional resources compared to item memory recognition (Troyer et al., 1999; Troyer & Craik, 2000), it is likely that spontaneous dips in attention levels prior to stimulus presentation may differentially impact context memory relative to item memory, however this assumption has not yet been tested to our knowledge. Additionally, it is important to note that results from the above studies combining adaptive SART and memory paradigms must be interpreted with caution. Criticism has been raised over the potential influence of speed-accuracy-trade-offs regarding the SART task. That is, errors of commission on the SART (responding to a NOGO stimulus), may in fact reflect individual differences in response speed strategies rather than compromised attentional state per se (Helton, 2009; Helton et al., 2009; Seli et al., 2012; Seli, et al., 2013a; Seli, et al., 2013b). For example, Seli et al., (2013b) demonstrated that errors of commission on the SART varied systematically with manipulated differences in response delay, in that, slower responses generated fewer errors. This suggests that SART errors may not merely reflect failures in attention per se, but are significantly impacted by individual differences in speed-accuracy-trade-offs. Finally, while SART allows for investigating how pre-stimulus attention levels impacts encoding success, the task only provides a behavioural marker for pre-stimulus attention on non-frequent target events rather than on every event, thus, it may not capture variation in pre-stimulus attention on a trial-by-trial basis, nor does it capture attentional variation during the presentation of events to be encoded.

While behavioural studies have significantly enriched our understanding on how attention shapes episodic memory encoding, the advent of neuroimaging has provided additional insight on the nature of the neural mechanisms involved. These mechanisms have mostly been inferred indirectly by studies that compare brain regions that respond differentially during the encoding of items that are subsequently remembered vs. forgotten (Brewer, 1998; Kim, 2011; Wagner et al., 1998). The difference in the neural response to subsequently remembered vs. forgotten items has often been attributed to differences in elaborative encoding operations and enhanced attention to subsequently remembered items (Chun & Johnson, 2011; Kim, 2011; Turk-Browne et al., 2006). One study using this paradigm showed that functional connectivity between parietal brain regions mediating attention, and posterior perceptual cortices at encoding was stronger during cue presentations associated with subsequently remembered versus forgotten items (Uncapher et al., 2011). This finding is consistent with other studies demonstrating that the brain state occurring prior to a presentation of a stimulus likely mediated by attentional factors, impacts memory formation for that stimulus (Fernandez et al., 1999; Guderian et al., 2009; Otten et al., 2006; Turk-Browne et al., 2006; Yoo et al., 2012), and dovetails with behavioural studies of pre-stimulus attention discussed above suggesting that attention may dictate whether a stimulus would be successfully encoded during a preparatory period even before the stimulus is presented. Other studies investigating the neural underpinnings of the role of attention in episodic memory encoding have relied on dual-task paradigms (Kensinger et al., 2003; Uncapher & Rugg, 2005). In general, these studies demonstrate that encoding under divided attention conditions reduce the likelihood of recruiting frontal and medial temporal lobe regions that are normally involved in successful encoding, thereby reducing the probability of engaging the encoding operations that support later episodic memory.

Biased competition models of attention (Beck & Kastner, 2009; Desimone & Duncan, 1995) have shed further light on how interruptions of attention at encoding may impair subsequent memory recall. According to these models, task relevant information is more robustly represented in sensory areas of the brain, and thus are more likely to fare better in competition with task-irrelevant information for downstream processing. Indeed, there is extensive evidence showing that attention enhances overall activity in visual cortical areas in response to attended vs. unattended features and locations (Gilbert & Li, 2013; Maunsell & Treue, 2006). In relation to episodic memory encoding, enhanced sensory representation of attended information may therefore increase the likelihood that higher fidelity representations will project to the medial temporal lobe for contextual binding leading to successful encoding (Uncapher & Rugg, 2009). Indeed, emerging evidence suggests that attention modulates medial temporal lobe areas that provide input to the hippocampus (Aly & Turk-Browne, 2016).

In contrast to task-induced activations related to attention that underlie successful encoding, deactivations in a set of midline brain regions such as the medial prefrontal cortex and posterior cingulate cortex (PCC), in addition to the lateral parietal cortices, are also associated with encoding success (Daselaar et al., 2004). These brain regions overlap considerably with the default-mode network (DMN), a network of regions that is deactivated during tasks that demand externally focused attention (Buckner et al., 2008; Raichle et al., 2001), and is often labelled as a 'task-negative' network (Fox et al., 2005). For instance, increased sustained attention is associated with greater deactivation of the DMN (Lawrence et al., 2003), whereas momentary lapses in attention are associated with less task-induced DMN deactivation (Weissman et al., 2006). Contrary to the notion that DMN reflects a 'task-negative' network, increased DMN activity may be observed in situations where attention is directed internally, such as during episodic retrieval, mind-wandering, and planning for the future (Buckner et al., 2008; Spreng, 2012). As such, task-induced DMN deactivation may reflect the suppression of one's attention to internal and self-oriented processes, and the allocation of neural and mental resources towards performance of tasks involving external stimuli (Anticevic et al., 2012). In relation to episodic memory encoding, increased deactivation of DMN regions may promote the allocation of attentional resources towards encoding of external stimuli, thereby supporting the successful associative binding of items to their contextual details, and thus better subsequent memory performance.

In the current study, we created a novel task, which we refer to as the *Attention at Encoding Task* (AET). This task was based off the commonly used psychomotor vigilance task (PVT: Dinges & Powell, 1985), which assesses vigilance/sustained attention and has been used extensively in sleep deprivation studies. We adapted the PVT in the current study to investigate whether and how spontaneous drifts in pre-stimulus attention and attention during encoding events, impact memory performance for items and their associative spatial context on a trial-by-trial basis. We also examined the neural underpinnings of the AET task, and investigated whether or not, and how variation in attention prior to or during an encoding event, modulate encoding-related activity. A typical PVT task measures variation in attention by recording RTs to visual or auditory stimuli that occur frequently at random intervals over a period of time. Relatively longer RTs on a trial-by-trial basis have been suggested to reflect instances where the participant's attention may have waned (Dorrian et al., 2004; Jung et al., 2011; Lim & Dinges, 2008). In the current AET design, we presented participants with pictures of objects either on the left or the right side of a screen while lying in an fMRI scanner, and asked them to remember the objects and their location. Prior to every object presentation trial, participants had to respond to a fixation cross that expanded in size after a random duration. Therefore, the object stimuli were staggered between the expanding fixation trials such that each object stimulus to be encoded had an associated reaction time measure for the fixation cross prior to that object (pre-stimulus RT) and following it (post-stimulus RT). We operationalize the state of attention at encoding as variability in RT. Specifically, variations in RT were used to index within-subject attentional state during the encoding phase such that relatively longer RT on a trial-by-trial basis would indicate a brief interruption in attention. Pre-stim RTs indexed attentional state prior to the object stimuli, while post-stim RTs indexed attentional levels during the presentation of an object stimulus or shortly after leading to the behavioural response. The memory for the objects and their associated location were tested at a later retrieval phase. We use pre- and post-stimulus RTs on a trial-by-trial basis to predict subsequent memory performance for the objects and their spatial context within-participant. If momentary failures in attention prior to or during the presentation of encoding events interrupts successful encoding operations, then we predict that relatively longer pre-stimulus RTs and/or post-stimulus RTs respectively, indexing spontaneous dips in levels of attention, will incur greater costs in memory failures for spatial context memory compared to item memory. Momentary dips in levels of attention would also be associated with attenuated encoding-induced functional activity for object-location associations as well as less deactivation of DMN regions.

2.3 Methods

2.3.1 Participants

Thirty-four healthy young adults (21-34 yrs) successfully completed this study. A statistical power analysis was performed for sample size estimation, based on previous investigations of attention and memory performance at encoding effects (Troyer & Craik, 2000)

(N = 24). The effect size (cohen'd valaue) was 1.49, considered to be very large using Cohen's criteria (1988). With an alpha = .05 and power = .08, the projected sample size needed with this effect size is approximately N = 12 for this within-group comparison. Thus, our sample size of 34 will be more than adequate for the main objectives of this study and should allow some buffer for expected post-hoc exclusion. A total of four participants were excluded from our analysis post-hoc. Three participants were excluded due to missing too many responses at encoding, and one participant was excluded for having an unusually slow mean response time (RT) at encoding and hence may not have been following task instructions. Post-hoc exclusion was based on meeting the 1.5 * Inter quartile range outlier rule. The final sample consisted of 30 participants (age range 21-34 yrs, mean age = 25.76 yrs; 17 females; mean years of formal education [EDU] = 15.80 yrs). All eligible participants underwent fMRI brain scanning while performing both encoding and retrieval phases of the task.

The study involved two sessions, each conducted on a separate day. Session 1 consisted of a medical questionnaire, a battery of neuropsychological tests, and a practice run of the AET performed in a mock MRI scanner. The Beck Depression Inventory (BDI-II), exclusion cut-off > 14, (Beck et al., 1996) and the California Verbal Learning Test (CVLT) Delay Free Recall (DFR) , exclusion cut-off < 11 (Mervielde et al., 1999) were used to assess eligibility. Additional exclusion criteria based on the medical questionnaire responses included: having a history of psychiatric illness, substance abuse, and/or neurological insult resulting in a loss of consciousness of > 1 minute. During session 1, participants also completed the CVLT Delay Cued Recall (DCR), and CVLT Delay Recognition (DRG) to assess long term verbal memory (Mervielde et al., 1999). To assess executive function, the computerized version of the Wisconsin Card Sorting Test (Berg Card Sorting Test: BCST; Mueller & Piper, 2014) 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. To assess the frequency of everyday attentional lapses, the Cognitive Failure Questionnaire (CFQ; Broadbent et al., 1982) and the Mindful Attention Awareness Scale-Lapses Only (MAAS-LO; Carriere et al., 2008) were administered.

Those who met the medical inclusion criteria, BDI-II and the CVLT cut-offs, and performed above chance on the mock-MRI scanner trials, were invited to participate in a second fMRI testing session where they were scanned during both encoding and retrieval portions of the AET task. All participants were recruited via online and printed advertisements from within the Greater Montreal region. Participants were paid and provided their informed consent to participate in the study. The ethics board of the Douglas Research Centre, Le Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de-l'Île-de-Montréal approved the study protocol.

2.3.2 Behavioural methods

To explore the effects of pre-stimulus attention and attention during encoding events on item and spatial context memory performance, we created the AET task (see **Figure 2.1**). Participants were asked to encode pictures of objects and their location on each trial, and to respond to a fixation cross that expanded in size after a random duration. They were then subsequently presented with a retrieval run consisting of an equal number of old and new objects intermixed at random, and their memory for the objects previously seen was tested. In total, participants completed 4 experimental runs of encoding and 4 runs of retrieval. Each encoding run was subsequently followed by its respective retrieval run with a brief distraction task between the encoding and retrieval phases (details discussed below). The order of run presentation was counterbalanced across participants.

Figure 2.1 AET task procedure

AET included an encoding and retrieval phase. On each encoding trial, participants were presented with a fixation cross that expanded in size and were asked to respond to the change in size as quickly as possible. An object stimulus to be encoded followed either on the left or right side of the screen and participants had to encode the object and its location. Response times to the fixation cross were used to attention levels on a trial-by-trial basis. On each retrieval trial, a centrally presented old or new object was shown and participants had to indicate whether the object was previously presented on the left, right, whether it was an old object but they don't remember its initial location, or whether it's a new object.

The task stimuli set was obtained from the freely available Bank of Standardized Stimuli (BOSS; Brodeur et al., 2014), which offers high quality and standardized images of objects, and has been used in several other behavioural and neuroimaging studies. Each encoding run consisted of objects (48 in total) randomly presented either on the left (24 objects) or right (24 objects) side of the screen. These objects were equally selected from 12 different categories (i.e.; food, musical instruments, vehicles, building infrastructure, clothing, decoration and gift, electronics, game and entertainment, household articles, kitchen items, outdoor and sport equipment, and stationary items). Similarly, each retrieval run consisted of a balanced distribution of objects selected from the same 12 categories (48 old and 48 new objects). Upon completion of all runs of the task, participants were asked to complete the Thinking Content component of the Dundee Stress State Questionnaire (DSSQ; Mervielde et al., 1999) to assess mind-wandering during the task. The task was programmed and run using E-Prime (Psychology Software Tools, Inc.; Pittsburgh, PA, USA) software. Participants requiring visual acuity correction wore corrective plastic lenses and two fiber optic 4-button response boxes were supplied to participants to make responses during the task. To ensure that responding to the fixation cross was indeed a valid index of attention, we computed an error rate for each participant (i.e., trials where participants failed to respond to the fixation cross divided by total number of encoding trials completed) and ran GLMs to determine if the error rate predicted scores on the attentional lapses questionnaires (CFQ, DSSQ, and MASS-LO), and memory accuracy on the AET.

2.3.3 Encoding phase

Each encoding trial commenced with a small fixation cross which was presented in the middle of the screen and increased in size after a random duration (2, 4, or 6 secs). The large fixation cross lasted on the screen for 200 msec then collapsed back to its original size and lasted for another 2 secs before commencing a new trial. Participants were asked to press a button as fast as possible when they detect the change in fixation cross size. This was followed by an object randomly presented either on the left or right side of the screen for 2 secs. Participants had to memorize the object and its location. Therefore, the instructions were to memorize the objects and their location, and to respond to the change in fixation cross size. These two sets of instructions were emphasized equally prior to beginning each run. The initial small variable fixation cross served to introduce jitter to the fMRI acquisition, and to prevent stimulus expectancy effects similar to the PVT (Dinges & Powell, 1985). Trial-by-trial variation in RT to the fixation cross size change was used to gauge attention levels. The encoding phase consisted of 4 runs (48 stimuli/run) for a total of 192 stimuli across all runs. Following each encoding run, participants completed a short distraction task (60 secs) to minimize rehearsal of encoded information before commencing the retrieval run. During the distraction phase, participants were simultaneously shown two words and were asked to select the word that comes first in the alphabet.

2.3.3 Retrieval phase

On each retrieval trial, participants were shown either an old (previously presented during encoding), or new object presented centrally for 3 secs. For each object they were asked to indicate whether the object was either i) previously presented on the left side; ii) previously presented on the right side; iii) an old object, but not sure of its initial location; iv) a new object. Trials were separated by a variable ITI fixation (2, 4, or 6 secs). This design allowed for the distinction between associative context retrieval and item memory retrieval without its spatial context. Each retrieval run consisted of 96 objects (48 old and 48 new) for a total of 384 objects across all 4 retrieval runs.

2.3.4 Behavioural data analysis

We calculated the proportion of different response types:

1. Associative context hits: Correctly recalling an object and its spatial location.
2. Item memory: Recognizing old objects but providing no associative spatial location.
3. Context misattribution: Recognizing old objects but providing incorrect associative spatial location (e.g., saying an object previously seen on the left was initially presented on the right).
4. Miss: Incorrectly identifying old objects as new.

5. Correct rejection: Correctly identifying new objects.
6. False alarm: Incorrectly identifying new objects as old.

The percentage of associative context hits, item memory and context misattribution were calculated as the number of responses in each respective category, divided by the total number of old hits completed per participant. The percentage of correct rejection and false alarms were calculated as the number of trials in each of the two categories, divided by the total number of new trials completed per participant. Trials where participants failed to respond at retrieval (3.31% out of the total retrieval trials completed) were excluded from the analysis. We computed overall accuracy (i.e., hits) as the sum of associative context hits, item memory and context misattribution, divided by the total number of old trials completed per participant. We also computed proportion associative context hits (correct associative context trials/total no. of hits), and proportion item memory (item memory trials/total no. of hits) as well as adjust context recollection accuracy. The adjusted contrast recollection accuracy scores were calculated as follows: Z(context hits) – Z(context misattributions). This accuracy measure adjusts the context memory task accuracy for false alarms. D' was used as a measure of sensitivity and was computed as overall standardized hit rate minus standardized false alarm rate. Finally, we computed coefficient of variation in RT as a measure of variability in attention during the task. This was calculated as the standard deviation in RT divided by mean RT within-participant. The coefficient of variation expresses the standard deviation as a percentage of mean performance level. We chose the coefficient of variation as a measure of RT variability as it is unbiased with respect to differences in mean RT levels across participants.

To ensure that participants scored above chance level, we conducted one-sample t-tests on hits, associative hits, and correct rejection. In addition to using d' as a measure of response discriminability, we calculated chance level based on response probability (i.e., probability of selecting the correct response by chance), and stimulus presentation probability (i.e., probability of a stimulus type appearing by chance) (Snytte et al., 2020). For example, response probability for hits = 75% (three out of 4 button responses would lead to a general hit i.e., old-left, old-right, old with no associated spatial location). On the other hand, stimulus presentation probability for hits would equal 50% (half of the stimuli presented at retrieval were old). Therefore, by compounding response and stimulus probability for hits, chance level would equal 37.5%. Chance level for correctly identifying an old item previously shown on the left or right was 6.25%. To calculate the overall chance level for associative context hits, we computed the sum of both probabilities (6.25% + 6.25%), which yielded 12.5%. Similar to associative context hits, chance level for correct rejection was computed as 12.5%.

R software (R Core Team, 2014) was used to conduct logistic regression analysis to test whether pre-stimulus attention and/or attention during encoding events differentially impact associative context versus item memory accuracy within-participant. Pre-stimulus attention levels ona trial-by-trial basis were indexed via RTs to the fixation cross preceding each object stimulus to be encoded, while attention levels during encoding events were indexed via RTs to the fixation cross following each object. For subsequent memory analysis, correct associative context trials were scored as 1, and item memory was scored as 0. Therefore, each encoding trial was associated with its respective pre-stimulus RT, post-stimulus RT and subsequent memory score (i.e., 1 for correct associative context and 0 for item memory). Trials with missing responses at encoding or retrieval, context misattribution trials, and miss trials were excluded from analysis. For each participant, a logistic regression analysis was conducted to predict the binary memory variable (i.e., 1, 0) from the RT index of pre-stimulus attention level during encoding. Another logistic regression analysis was conducted to predict the same binary memory variable from post-stimulus RT during encoding for each participant. Finally, we compared the resulting beta values for all participants via one sample t-test to determine their overall direction at the grouplevel.

We were also interested in testing whether variation in pre-stimulus attention, and attention levels during encoding events impacts associative context recollection more broadly. To that end, we ran a third within-participant logistic regression model testing whether pre-stimulus attention levels as indexed by pre-stimulus fixation RTs, would predict associative context hits, versus associative context failure (i.e., collapsing item memory, context misattribution, and miss events). The resulting beta values for all participants were then compared via one sample t-test to determine their overall direction at the group level. Lastly, we ran a fourth and final logistic regression model to predict associative context hits, versus associative context failure (i.e., collapsing item memory, context misattribution, and miss events) within-participant, from post stimulus RTs at encoding. The resulting beta values were then compared via one-sample t-tests to determine their overall direction at the group level.

Finally, we conducted an exploratory analysis to investigate whether environmental factors such as years of educational attainment (EDU) or estimated IQ based on the AMNART scale (Grober et al., 1991) may help explain some of the inter-individual variability in the effects of attention on AET memory performance across participants. To that end, we computed a composite measure of EDU and IQ as described in (Elshiekh et al., 2020). The mean value of z-scored education in years and z-scored estimated IQ based on the AMNART was calculated for each participant. We then ran GLMs to determine whether this measure predicts coefficient of variation in RT, AET memory performance, or beta values from significant logistic regression analyses.

2.3.5 MRI methods

MRI scanning was performed on a Siemens 3T Magnetom Prisma Fit scanner housed at the Douglas Institute Brain Imagining Centre. Participants were fitted with a standard 12-channel head coil while lying in supine position. At the beginning of each fMRI testing session, T1-weighted anatomical images were collected using a 3D gradient echo MPRAGE sequence (TR = 2300 msec, TE = 2.36 msec, flip angle = 9°, 192 1 mm sagittal slices, 1 x 1 x 1 mm voxels, FOV = 256 mm^2). BOLD fMRI images were acquired using Multiband T2*-weighted gradient Echo Planar Imaging (EPI) sequence (TR = 700 msec, TE = 30 msec, multiband factor = 4, flip angle = 48°, FOV = 252 mm^2, matrix size = 84 x 84, in plane resolution = 3 mm x 3 mm, 44 transverse 3 mm slices with no slice gaps) during the encoding and retrieval runs of the AET task. Acquisition sequences alternated between phase encoding in an anterior-posterior (AP) direction in one run, and phase encoding in a posterior-anterior (PA) direction in another run for every participant. This was performed to reduce the signal loss and distortions from the high-resolution multiband acquisition. Finally, split slice-GRAPPA (leak block) reconstruction algorithm was applied to correct for potential signal leakage during slice separation (unaliasing) to recover the whole brain volume (Risk et al., 2018).

The AET task was back projected onto a screen in the scanner bore and participants lying in the scanner were able to view the task via a mirror mounted within the standard head coil.

2.3.6 Pre-processing

Images were first converted from DICOM to NIFTI format. Statistical Parametric Mapping (SPM) version 12 software (https://www.fil.ion.ucl.ac.uk/spm/) run with MATLAB (www.mathworks.com) was used for pre-processing on a Linux platform. The first 17 scans (~ 12 secs) of every encoding and retrieval run were discarded to ensure that images have reached steady-state magnetization. Motion and distortion correction were performed using single-band reference images (SBREFs). All SBREFs acquired at the beginning of each run were first aligned to the SBREF of the first run. Subsequently, functional images within each run were aligned to the SBREF of that run. Re-alignment was performed using a 6-parameter rigid body spatial transform and a least squares approach. Functional images were also unwarped to correct the EPI artifacts due to magnetic field inhomogeneities. Runs with > 3mm movement were excluded from further analysis. In total, 10 runs were excluded from 8 participants. None of those participants had more than 2 runs excluded. Next, we registered the T1 image (source image) to the unwarped SBREF of the first run (keeping SBREF stationary) to reduce computational complexity. Given that multiband timeseries images have reduced tissue contrast (due to incomplete T1 relaxation), we used the SBREF image with full tissue contrast to register the structural data to the functional images. In order to maintain the T1 image resolution, re-slicing was not performed. Functional images were then segmented, skull stripped, and spatially normalized to Montreal Neurological Institute (MNI) space using tissue probability maps of gray matter, white matter and CSF (available in SPM12). Finally, images were smoothed with a 6 mm full-width half maximum (FWHM) isotropic Gaussian kernel. Our high-resolution, fast TR multiband sampling sequence reduces the need for slice timing correction since slices within each volume were acquired much closer together than in a typical fMRI acquisition sequence (TR ~ 2.5 secs). As such, no slice timing correction was employed in the current study.

2.3.7 fMRI GLM analysis with parametric modulation

The goal of our fMRI analysis was to investigate how pre- and post-stimulus RTs modulate encoding-related activity on a trial-by-trial basis. A general linear model (GLM) was applied to the time-series data using SPM 12 software. For each participant, we constructed two separate design matrices for contrast analysis and parametric modulation analysis. In the first design matrix, trial onsets for each of the following conditions were modelled with a separate regressor: encoding trials; retrieval trials with objects previously shown at encoding (retrieval-old); retrieval trials with new objects (retrieval-new); retrieval trials with no associated response (retrieval-no response). Only encoding trials with associated pre- and post-stimulus responses were modelled in the encoding trials regressor. Additionally, we included six head motion parameters (i.e., x, y, z, pitch, roll, and yaw) as nuisance regressors in the design matrix. Pre-stimulus RTs and post-stimulus RTs were entered as two separate parametric modulators in that order for the encoding trial onsets regressor to identify regions that modulate neural activity during encoding as an effect of pre- and post-RTs respectively. These parametric modulators allowed for examining regions whose activity correlated positively (i.e., increasing as RT increased) and negatively (i.e., decreasing as RT increased) with pre-stimulus RT or post-stimulus RT during encoding. The trial onset regressors and parametric modulators were convolved with the canonical hemodynamic response function (HRF).

The SPM software package automatically orthogonalizes parametric modulators in a hierarchical fashion such that each parametric regressor is orthogonalized with respect to the ones preceding it. Thus, results will vary depending on the order by which parametric regressors were entered in the model. In the GLM model described above, the parametric regressor for pre-stimulus RTs was specified first while the regressor for post-stimulus RTs was specified second.

Therefore, in that case, the regressor for pre-stimulus RTs was orthogonalized with respect to the unmodulated regressor (i.e., encoding trials onset). On the other hand, the regressor for post-stimulus RTs was orthogonalized with respect to the unmodulated regressor and the regressor for pre-stimulus RTs. Thus, the pre-stimulus RTs regressor in this model was not adjusted for post-stimulus RTs. Following recommendations by Mumford and colleagues (2015), we constructed a second GLM model identical to the first except for the order of how the parametric modulators were entered. In the second model, the regressor for encoding trial onsets was modulated by post-stimulus RTs as the first parametric regressor, and pre-stimulus RTs as the second parametric modulator. The pre-stimulus RTs regressor in this second model was therefore orthogonalized with respect to the unmodulated regressor and adjusted for post-stimulus RTs.

To identify task-related effects at encoding, we constructed the following contrasts 1) *Encoding* > *retrieval-old*: This contrast identified regions that were more active during encoding the object stimuli relative to retrieving them. 2) *Implicit baseline* > *encoding*: This contrast identified regions that were more active during the implicit baseline (unmodelled intertrial events) compared to encoding. In other words, this contrast identified regions that were deactivated at encoding compared to baseline and was used to identify DMN regions. The resulting contrast image from this contrast was compared against a canonical DMN map using a spatial correspondence ‘spin-test’ analysis (please see below) (Alexander-Bloch et al., 2018). This was performed to validate DMN regions in our data. The contrasts described above were independent from and unbiased by the parametric modulation and thus could be extracted from either GLM model.

To extract effects related to parametric modulation by pre-stimulus RTs, we created the following contrasts from the *second* GLM model: 1) *Pre-stimulus RTs* > *implicit baseline*: This contrast identified regions that showed greater activation with longer pre-stimulus RTs during encoding trials relative to baseline. 2) *Implicit baseline* > *Pre-stimulus RTs*: This contrast identified regions that showed less activation with longer pre-stimulus RTs during encoding trials relative to baseline.

To extract effects related to parametric modulation by post-stimulus RTs, we created the following contrasts from the *first* GLM model: 1) *Post-stimulus RTs* > *implicit baseline*: This contrast identified regions that showed greater activation with longer post-stimulus RTs during encoding trials relative to baseline. 2) *Implicit baseline* > *Post-stimulus RTs*: This contrast identified regions that showed less activation with longer post-stimulus RTs during encoding trials relative to baseline. The resulting contrast images from each of the aforementioned contrasts were entered into second-level analysis using a mixed effects model to allow for inferences at the group level. To correct for multiple comparisons, a cluster-based threshold for False Discovery Rate (FDR) of 5% was applied (Chumbley & Friston, 2009).

To investigate the prediction that longer pre-stimulus RTs and/or post-stimulus RTs would be associated with less activation of encoding-related regions, we performed a conjunction analysis where we used the thresholded voxel-wise map of the *encoding* > *retrieval-old* contrast as an inclusive mask, and overlayed it on top of the thresholded voxel-wise map of the *implicit baseline* > *pre-stimulus RTs* to determine clusters that were activated in both maps. Similarly we repeated the conjunction analysis masking the thresholded voxel-wise map of the *implicit baseline* > *post-stimulus RTs* with thresholded voxel-wise map of the *encoding* > *retrieval-old* contrast to determine effects related to post-stimulus RTs.

To test our prediction that longer pre-stimulus RTs/and or post-stimulus RTs would be associated with less deactivation of DMN regions at encoding, we performed a conjunction analysis such that the thresholded voxel-wise map of the *implicit baseline* > *encoding* contrast was used as an inclusive mask and was overlayed on top of the thresholded voxel-wise map of the *pre-stimulus RTs* > *implicit baseline* contrast to determine clusters that were activated in both maps. To determine effects related to post-stimulus RTs, we repeated this conjunction analysis masking the thresholded voxel-wise map of the *post-stimulus RTs* > *implicit baseline* with the thresholded voxel-wise map of the *implicit baseline* > *encoding* contrast.

We were also interested in exploring whether there were significant encoding-related clusters that were modulated positively by pre-stimulus RTs or post-stimulus RTs (i.e., areas that showed a greater activity with longer pre-stimulus RTs or post-stimulus RTs respectively at encoding relative to retrieval). To that end, we performed a conjunction analysis where the thresholded voxel-wise map of the *pre-stimulus RTs* > *implicit baseline* was masked inclusively by the thresholded voxel-wise map of the *encoding* > *retrieval-old* contrast to determine clusters of activation common to both maps. Similarly, we repeated this conjunction analysis masking the thresholded voxel-wise map of the *post-stimulus RTs* > *implicit baseline* by the thresholded voxel-wise map of the *encoding* > *retrieval-old* contrast to determine effects related to post-stimulus RTs.

2.3.8 Spatial correspondence test

We performed a spatial correspondence 'spin' test (Alexander-Bloch et al., 2018) on the *implicit baseline* > *encoding* contrast image in order to validate DMN regions identified from the contrast. We first extracted the DMN ROIs from the Yeo's 7 Network Atlas (Yeo et al., 2011). Spatial correspondence was then assessed between the extracted DMN atlas and the t-map contrast image output of the *implicit baseline* > *encoding* contrast from SPM. Both the atlas and the t-map were projected onto FreeSurfer's average surface fsaverage5 by using nearest neighbour interpolation to project the maps onto the middle of the cortical surface, which lies at 50% between the white and pial surface. We used Normalized Mutual Information (NMI) as the correspondence statistic to assess spatial overlap (Bettinardi, 2021). The NMI ranges from 0 to 1 where 0 implies that the partitions are completely independent and 1 meaning that they are identical. A 1000 spin permutations were generated to test for statistical significance and a p-value was estimated as the number of times that the permuted NMI exceeded the original NMI. Additionally, we performed a spatial correspondence test between the *implicit baseline* > *encoding* contrast image output and each of the remaining 6 canonical networks from the Yeo Atlas (i.e., visual, somatomotor, dorsal attention, salience, limbic, and frontoparietal networks) in order to determine what additional functional networks were revealed by the aforementioned contrast.

2.3.9 Post-hoc brain-behaviour ROI correlations

Our results (discussed in detail below) revealed a significant cluster of activation in the visual cortex for the following conjunction analysis: Voxel-wise map of *post-stimulus RTs* > *implicit baseline* contrast, masked by *voxel-wise map of encoding* > *retrieval-old* contrast. We also found a significant cluster in the superior frontal gyrus from the following conjunction analysis: Voxel-wise map of *implicit baseline* > *post-stimulus RTs* contrast, masked by *voxel-wise map of implicit baseline* > *encoding.* We were interested in performing ROI analysis on those clusters in order to better understand how their activation pattern was linked to associative context memory performance on the AET task and whether this pattern was modulated by differences in EDU/IQ. To interrogate the cluster of activation in the visual cortex further, we first extracted contrast estimates from each voxel in that cluster for each participant from the *encoding* > *retrieval-old* contrast. We then averaged those estimates over all the voxels in the cluster for each participant. Hence, an average contrast estimate from the significant visual cluster ofactivation was obtained for each participant. We then ran GLMs to determine whether adjusted context recollection accuracy scores and the composite measure of EDU/IQ predicted the average contrast estimate scores. This was done to investigate how this pattern of activation relates to task performance and whether some of the variance in this pattern of activation across participant s can be explained by environmental factors such EDU and IQ. We followed the same procedure to perform ROI brain-behaviour correlations on the significant superior frontal gyrus cluster. After extracting contrast estimates from the *implicit baseline* > *encoding* contrast averaged across all the voxels in the superior frontal gyrus cluster for each participant, we ran GLMsto determine whether those estimates can be predicted by participants' adjusted context recollection accuracy scores as well as the composite measure of EDU and IQ.

2.4 Results

2.4.1 Accuracy and reaction time results

Table 2.1 summarizes demographics and neuropsychological test data, and **Figure 2.2a** shows a violin plot of accuracy results on the AET. Participants scored well above chance level on associative context hits (M = .56, SD = .20, t(29) = 12.17, p < .001, hits (M = .78, SD = .14, t(29) = 15.77, p < .001), and correct rejection (M = .85, SD = .20, t(29) = 34.57, p < .001). Means and SDs of accuracy results are presented in **Table 2.2**

Table 2.1 Demographics and neuropsychological test data

Sample size	30
Age (Yrs)	25.76 (0.77)
Gender (n, [%] females)	17 [57%]
EDU (Yrs)	15.80 (0.35)
CVLT – DFR ^{b}	12.63 (0.32)
CVLT – DCR	12.87 (0.36)
CVLT – DRG	15.23 (0.18)

WCST – categories completed [c]	8.00 (0.27)
WCST – % correct [c]	0.81 (1.88)
D-KEFS – LF	37.20 (1.71)
D-KEFS – CF [d]	35.83 (1.63)
D-KEFS – CS	14.23 (0.51)
Estimated IQ (AMNART)	112.80 (1.45)
CFQ – Total score	29.63 (1.99)
CFQ – Forgetfulness	10.57 (0.82)
CFQ – Distractibility	11.10 (0.86)
CFQ – False triggering	6.67 (0.62)
MASS – Lapses	30.33 (1.33)
DSSQ – TRI	20.53 (1.08)
DSSQ - TUI	14.63 (0.94)

Note: This table presents means and standard deviations between brackets for demographic, neuropsychological measures. 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; CFQ = Cognitive failures Questionnaire; MASS = Mindful Attention Awareness Scale (lapses only); DSSQ = Dundee Stress State Questionnaire; TRI = Task-related Interference; TUI = Task-unrelated Interference.

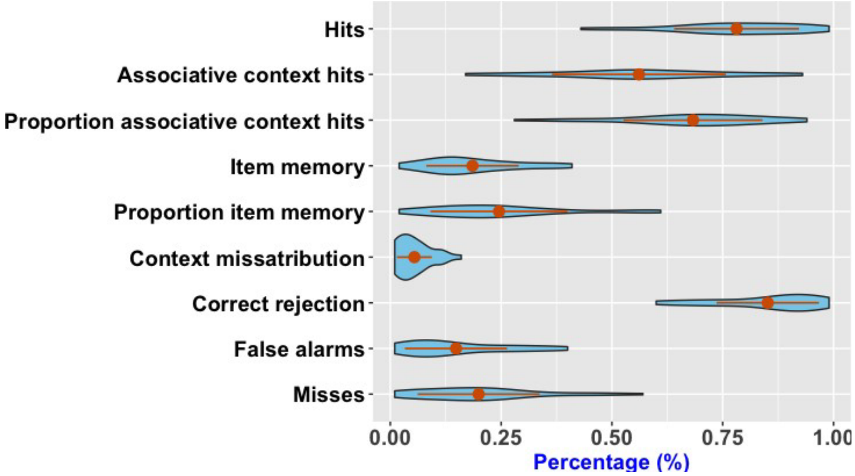
Table 2.2 AET task accuracy results

Hits	.78 (.14)
Associative context hits	.56 (.20)
Proportion associative context hits	.68 (.16)
Item memory	.19 (.10)
Proportion Item memory	.25 (.15)
Context misattribution	.05 (.04)
Correct rejection	.85 (.20)
False alarms	.15 (.12)
Misses	.20 (.14)
d’	2.08 (.97)

Note: This table presents means and standard deviations between brackets for accuracy results for the AET task.

The mean RT to the fixation cross staggered between the object stimuli at encoding was 373.68 msec (SD = 57.51) and mean coefficient of variation in RT was 0.34 (SD = .07). **Figure 2.2b** displays a bar plot of mean pre-stimulus RT to objects that were subsequently scored as associative context hit, item memory, context misattribution, miss, and associative context failure (i.e., collapsing item memory, context misattribution, and miss events). **Figure 2.2c** displays a bar plot of mean post-stimulus RT to objects that were subsequently scored as associative context hit, item memory, context misattribution, miss, and associative context failure. Post-hoc tests revealed that mean pre-stimulus RTs associated with the different stimulus categories were not significantly different from each other. Similarly, mean post-stimulus RTs associated with the different stimulus categories were not significantly different from each other. There were no sex differences across participants in AET memory performance or mean RT of fixation cross at encoding (ps > .05). Overall, participants performed the task well as indicated by a relatively low error rate (M = 2.34%, SD = 2.80) and high d' value (M = 2.08, SD = 0.97) reflecting high task sensitivity. Error rate did not predict task accuracy (p > .05), yet, it predicted distractibility as measured by CFQ (F(1, 28) = 4.761, p = .038, R^2 = .145), and showed a marginally significant positive association with task unrelated interference – DSSQ (p = .078). The composite measure of EDU/IQ did not significantly predict memory performance (i.e., hits or adjusted context memory performance), variation in attention (i.e., coefficient of variation in RT), or beta values from logistic regression analyses (ps > .05).

a)


Hits
Associative context hits
Proportion associative context hits
Item memory
Proportion item memory
Context missatribution
Correct rejection
False alarms
Misses
0.00
0.25
0.50
0.75
1.0
Percentage (%)

b)


Associative context hits
Item memory
Context missatribution
Miss
Associative context failure
0
200
400
600
Reaction times (msec)

c)

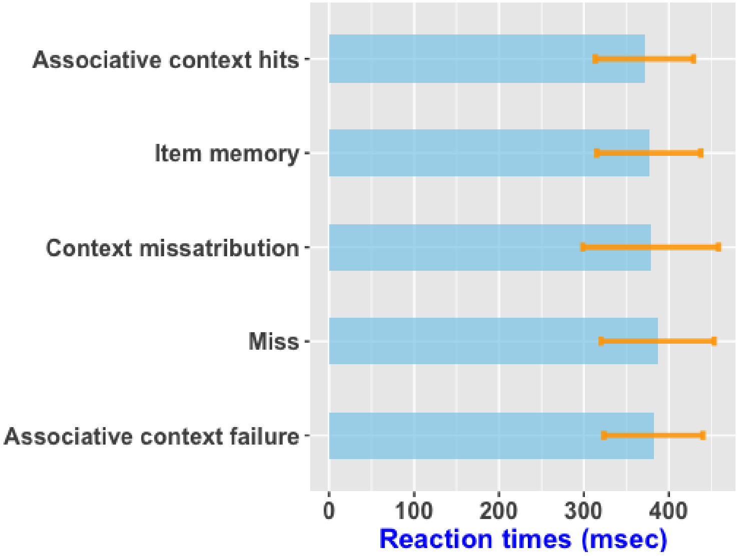


Figure 2.2 Plots of accuracy and response times for AET task

a) Violin plot showing mean accuracy results and standard deviations for each event category on the AET task. Participants scored well above chance level on hits, associative context hits, and correct rejection. Associative context memory hits percentage was significantly greater than item memory. b) Bar plot showing mean response time and standard deviations to the variable fixation cross presented prior to stimuli that were subsequently scored as associative context hit, item memory, context misattribution, miss, and associative context memory failure (i.e, collapsing item memory, context misattribution, and miss events). The mean response times for the different stimulus categories were not significantly different from each other. c) Bar plot showing mean response time and standard deviations to the variable fixation cross presented after stimuli that were subsequently scored as associative context hit, item memory, context misattribution, miss, and associative context memory failure (i.e, collapsing item memory, context misattribution, and miss events). The mean response times for the different stimulus categories were not significantly different from each other.

2.4.2 Logistic regression analysis results

We first evaluated the relationship between our RT index of pre-stimulus attentional state at encoding, and associative context and item memory accuracy at retrieval. We used logistic regression to evaluate this relationship within-participant, and then compared the resulting beta values to determine their overall direction at the group level. Shapiro-Wilks test showed that the data did not violate assumptions of normality (p = .92), and one sample t-test performed at the group level revealed that the overall direction of the betas was not different than zero (p = .72). We ran another logistic regression model testing whether variation in pre-stimulus attention levels at encoding would predict associative context memory more broadly (i.e., associative context success vs. associative context failure). Shapiro-Wilks test showed that the data did not violate assumptions of normality (p = .84), and one sample t-test performed at the group level revealed that the overall direction of the betas was not different than zero (p = .09). Taken together, these results suggest that variation in pre-stimulus attention levels as indexed by RTs to fixations presented prior to object stimuli to be encoded, did not impact associative context vs. item memory performance, nor did they predict associative context hits versus associative context failure more broadly.

Similar to the analyses outlined above, we ran within-participant logistic regressions to evaluate whether post-stimulus RTs predicted associative context hits vs. item memory, and then compared the resulting beta values to determine their overall direction at the group level. Shapiro-Wilks test showed that the data did not violate assumptions of normality (p = .07), and one sample t-test performed at the group level revealed that the overall direction of the betas was not different than zero (p = .18). Hence, post-stimulus RTs failed to predict associative context hits vs. item memory. Our final within-participant logistic regression analysis tested whether post-stimulus RTs would predict associative context hits vs. associative context failure more broadly. Our results revealed that the majority of the participants (20/30) showed negative beta values, indicating that quicker post-stimulus RTs at encoding predicted associative context hits, and slower post-stimulus RTs predicted associative context failure. To test whether this relationship holds at the group level, we ran a one sample t-test to determine the overall direction of the beta values after making sure that the data did not violate assumptions of normality

(Shapiro-Wilks test: p = .43). The logistic functions for all participants are plotted in **Figure 2.3**, revealing a reliably negative slope on average (p = .01), indicating that faster RT to the fixation cross that ensued the object stimuli predicted associative context memory success, and slower post-stimulus RTs predicted associative context failure at retrieval. We also compared the two groups of participants showing positive (n=10), and negative (n=20) slopes on AET memory performance. Results showed that participants with negative slopes had higher hits rate (t(28) = -2.59, p = .02), and associative context memory accuracy (t(28) = -2.20, p = .03), compared to those with positive slopes.

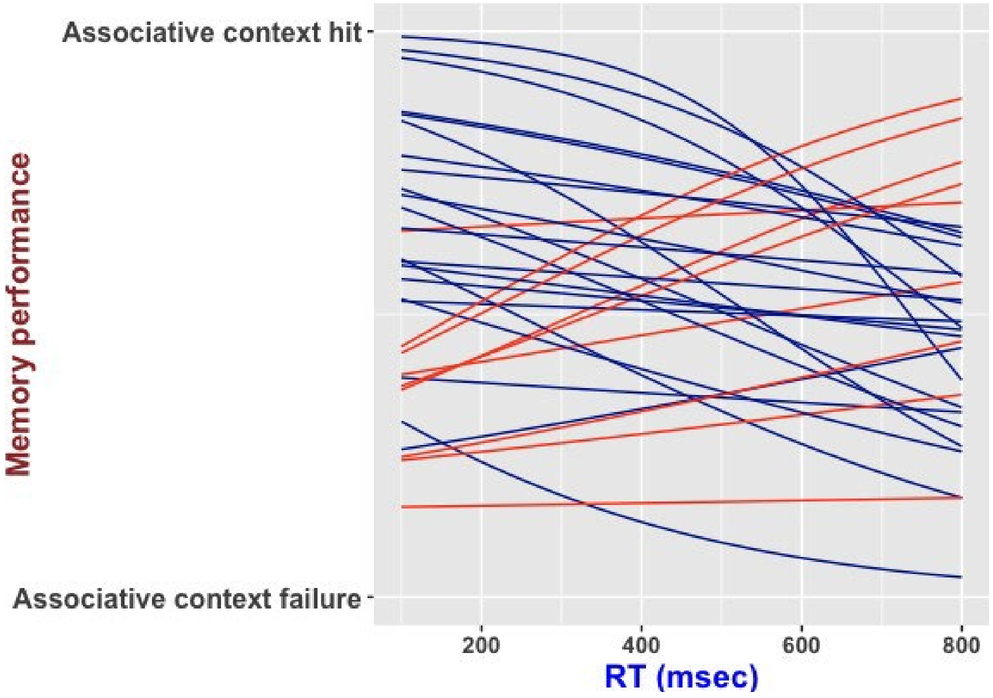


Figure 2.3 Logistic functions of all participants predicting associative context success vs. associative context failure from post-stimulus RTs

The logistic function for each participant is plotted on the same graph to visualize the relationship between post-stimulus encoding response times, and associative context success vs. associative context failure. Red lines demonstrate logistic functions with positive slopes and blue lines demonstrate logistic functions with negative slopes. As indicated on the graph, the majority of participants (20/30) had negative slopes indicating a reliably negative slope on average (p = .01). That is, faster post-stimulus response times at encoding predicted associative context memory success, and slower post-stimulus response times predicted associative context memory failure.

2.4.3 fMRI results

As revealed by our fMRI GLM analysis, the *encoding* > *retrieval-old* contrast showed significant clusters of activation in primary and secondary visual cortex (BA 17/18/19), superior frontal regions (BA 8/9), left ventro-lateral prefrontal cortex (BA 45/47), lateral temporal cortex (BA 21/22/38) as well as other regions. These clusters were more active during the encoding condition relative to the retrieval-old condition. **Table 2.3** outlines the local maxima and **Figure 2.4** displays the SPM activation map for this contrast.

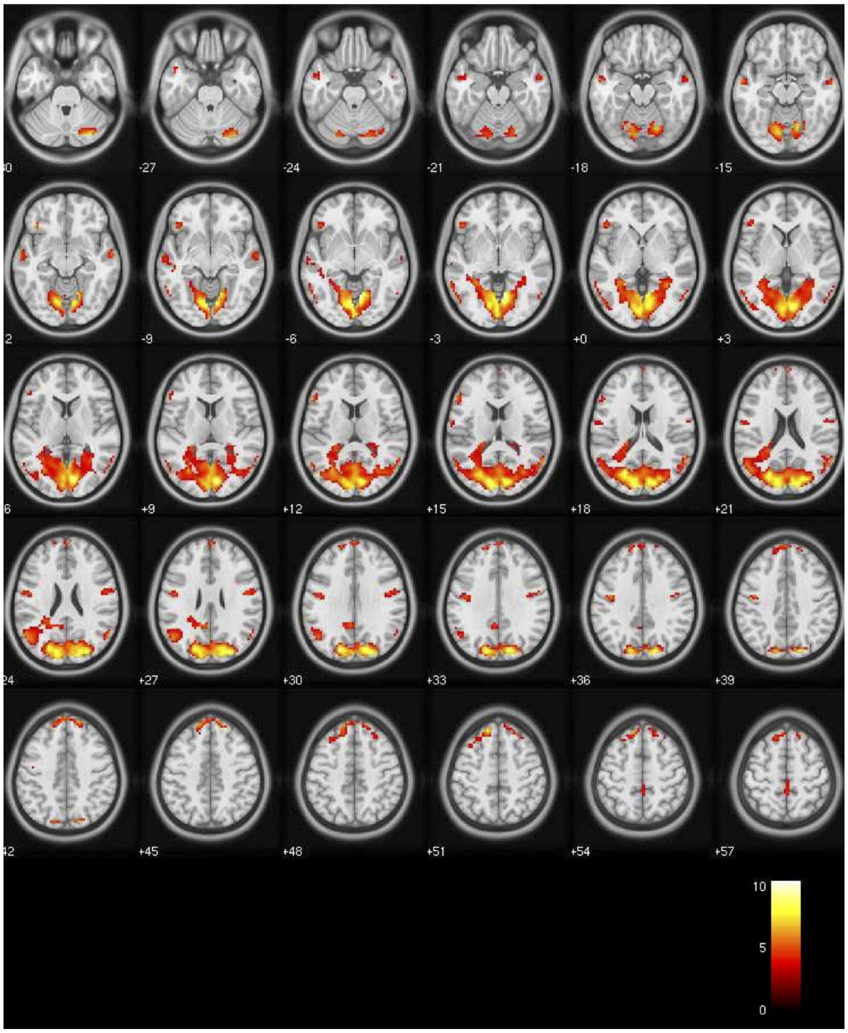


Figure 2.4 SPM activation map for Encoding > Retrieval-old contrast

This SPM activation map displays regions that were more active during encoding object-location associations relative to retrieving old objects. Results are illustrated with a montage of axial slices varying between MNI-z = -30 to MNI-z = +57 and a cluster-based threshold for FDR of 5% was applied to correct for multiple comparisons.

Table 2.3 Brain regions showing higher activity at encoding relative to retrieval (*Encoding > Retrieval-old* contrast)

	Cluster level				Peak level					
ROI	P FWE-corr	P FDR-corr	K_E	P unc	P FWE-corr	P FDR-corr	T	P unc	x,y,z {mm}	Gyral location (BA) *(Left-L, Right-R)*
1	**0.000**	**0.000**	**3640**	**0.000**	**0.000**	**0.000**	**10.43**	**0.000**	**9 -85 8**	**R-cuneus (17)**
					0.000	0.000	10.00	0.000	9 -64 -4	R-lingual (18)
					0.000	0.000	9.58	0.000	-18 -82 32	R-cuneus (19)
2	**0.000**	**0.000**	**291**	**0.000**	**0.000**	**0.000**	**8.11**	**0.000**	**-15 38 50**	**L-superior frontal (8)**
					0.005	0.005	6.62	0.000	18 50 41	R-superior frontal (9)
					0.024	0.016	6.01	0.000	-15 47 44	L-superior frontal (8)
3	**0.013**	**0.011**	**73**	**0.002**	**0.01**	**0.008**	**6.37**	**0.000**	**-42 26 -13**	**L-Inferior frontal (47)**
					0.057	0.029	5.62	0.000	-48 29 -4	L-Inferior frontal (47)
					0.131	0.052	5.24	0.000	-54 26 14	L-Inferior frontal (45)
4	**0.013**	**0.011**	**73**	**0.002**	**0.018**	**0.013**	**6.13**	**0.000**	**-42 -10 35**	**L-inferior frontal (6)**
					0.097	0.045	5.38	0.000	-48 -7 26	L-inferior frontal (6)
					0.739	0.291	4.20	0.000	-60 -4 17	L-inferior frontal (6)
5	**0.021**	**0.014**	**65**	**0.003**	**0.03**	**0.018**	**5.92**	**0.000**	**-60 -7 -16**	**L-inferior temporal (21)**
					0.435	0.138	4.60	0.000	-48 5 -28	L-middle temporal (38)
6	**0.001**	**0.002**	**118**	**0.000**	**0.056**	**0.029**	**5.63**	**0.000**	**0 -22 71**	**Superior frontal (6)**
					0.324	0.108	4.78	0.000	6 -25 77	R-superior frontal (4)
7	**0.08**	**0.043**	**43**	**0.013**	**0.125**	**0.052**	**5.26**	**0.000**	**60 -10 -13**	R-superior temporal (22)
					0.57	0.189	4.42	0.000	54 -1 -22	R-middle temporal (22)
8	**0.03**	**0.018**	**59**	**0.005**	**0.218**	**0.074**	**4.99**	**0.000**	**45 -7 29**	**R-inferior frontal (6)**
					0.364	0.12	4.71	0.000	51 -4 23	R-inferior frontal (4)

The local maxima and SPM activation map for the *baseline* > *encoding* contrast are displayed in **Table 2.4** and **Figure 2.5** respectively. Significant clusters of activation include several DMN regions (Buckner et al., 2008) such as medial PFC (BA 6), posterior cingulate cortex (BA 23/31), and angular gyrus (BA 39). Furthermore, significant clusters of activation were also observed in the superior frontal gyrus (BA 6), and insula (BA 13). These regions were more active during implicit baseline relative to encoding. As such, the aforementioned regions showed task-induced deactivation at encoding. Spatial correspondence assessed by NMI in a permutation-based spin test analysis revealed significant spatial correspondence between the *baseline* > *encoding* contrast image and each of the DMN (NMI = .030, p < .001), sensorimotor (NMI = .025, p < .001), and salience (NMI = .065, p < .001) canonical functional networks as defined by the Yeo Atlas (Yeo et al., 2011).

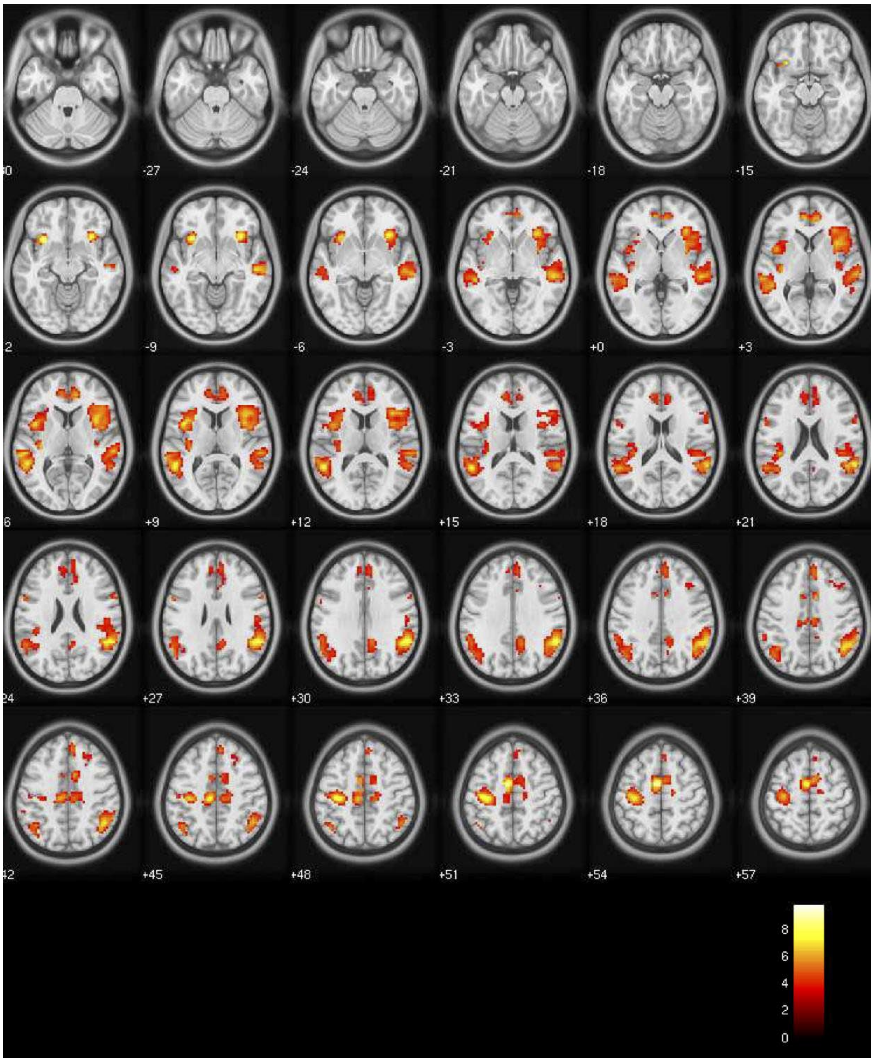


Figure 2.5 SPM activation map for Baseline > Encoding contrast

This SPM activation map displays regions that showed deactivation at encoding relative to implicit baseline. Results are illustrated with a montage of axial slices varying between MNI-z = -30 to MNI-z = +57 and a cluster-based threshold for FDR of 5% was applied to correct for multiple comparisons.

Table 2.4 Brain regions showing deactivations at encoding relative to implicit baseline (*Baseline* > *Encoding* contrast)

	Cluster level				Peak level					
ROI	P FWE-corr	P FDR-corr	K_E	P unc	P FWE-corr	P FDR-corr	T	P_{unc}	x,y,z {mm}	Gyral location (BA) *(Left-L, Right-R)*
1	**0.000**	**0.000**	**1255**	**0.000**	**0.000**	**0.000**	**9.79**	**0.000**	**-6 -4 53**	**L-superior frontal (6)**
					0.000	0.001	7.76	0.000	-33 -25 47	L-postcentral (1)
					0.000	0.001	7.59	0.000	-9 -25 44	L-posterior cingulate (31)
2	**0.000**	**0.000**	**320**	**0.000**	**0.000**	**0.000**	**8.90**	**0.000**	**-33 17 -13**	**L-insula (13)**
					0.000	0.001	7.66	0.000	-42 8 8	L-inferior frontal (44)
					0.096	0.032	5.36	0.000	-57 5 26	L-inferior frontal (6)
3	**0.000**	**0.000**	**873**	**0.000**	**0.000**	**0.000**	**8.52**	**0.000**	**-54 -52 11**	**L-angular gyrus (39)**
					0.002	0.003	6.95	0.000	-57 -31 5	L-superior temporal (21)
					0.003	0.003	6.84	0.000	-39 -31 20	L-supramarginal gyrus (40)
4	**0.000**	**0.000**	**1110**	**0.000**	**0.000**	**0.000**	**8.37**	**0.000**	**57 -49 32**	**R-angular gyrus (39)**
					0.000	0.000	8.19	0.000	60 -49 20	R-angular gyrus (39)
					0.001	0.002	7.15	0.000	45 -55 38	R-angular gyrus (39)
5	**0.000**	**0.000**	**618**	**0.000**	**0.000**	**0.000**	**8.09**	**0.000**	**30 20 -10**	**R-insula (13)**
					0.003	0.003	6.84	0.000	36 11 2	R-insula (13)
					0.005	0.004	6.61	0.000	33 29 -1	R-inferior frontal (47)
7	**0.008**	**0.003**	**85**	**0.001**	**0.03**	**0.013**	**5.89**	**0.000**	**12 -52 32**	**R-posterior cingulate (23)**
					0.57	0.189	4.42	0.000	54 -1 -22	R-middle temporal (21)
8	**0.121**	**0.047**	**38**	**0.020**	**0.791**	**0.289**	**4.11**	**0.000**	**27 29 41**	**R-middle frontal (8)**
					0.952	0.509	3.78	0.000	36 23 35	R-middle frontal (9)
					0.992	0.795	3.54	0.001	24 20 41	R-middle frontal (8)

Significant clusters of activation for the *post-stimulus RTs > implicit baseline* were observed in superior frontal gyrus (BA 31/6), primary visual cortex (BA 17/18), and supramarginal gyrus (BA 40). Encoding activation in these clusters was associated with longer post-stimulus RTs (relative to implicit baseline). **Table 2.5** outlines the local maxima and for this contrast. There were no significant clusters of activation observed for the *implicit baseline* >

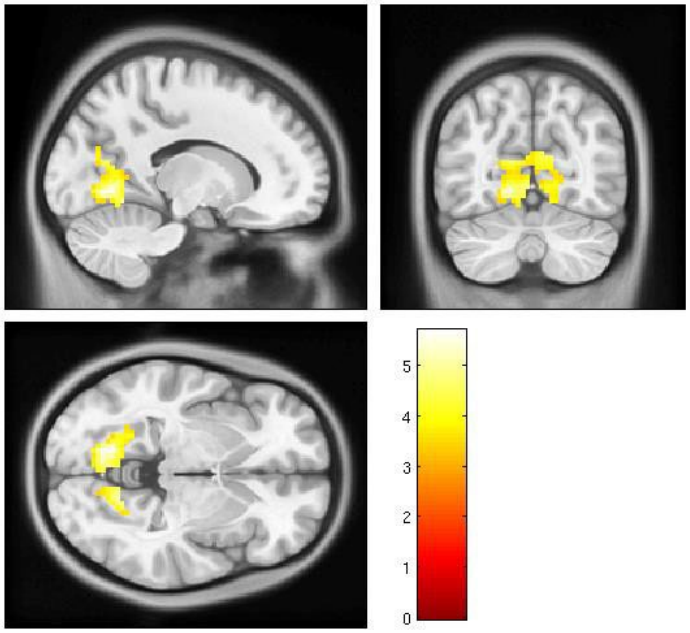
post-stimulus RTs that survived our FDR threshold. However, bilateral clusters of activation in the lateral occipital cortex (BA 18; peaks: -24 -94 -7, and 30 -91 -7) (See supplementary **Figure 2.8** and **Table 2.8**) were observed for this contrast at significance threshold of < 0.001 uncorrected. Additionally, no significant clusters of activation were observed for the contrasts examining activity modulation related to pre-stimulus RTs (i.e., *pre-stimulus RTs > implicit baseline,* and *implicit baseline > pre-stimulus RTs* contrasts).

Table 2.5 Brain regions showing higher activity with longer post-stimulus RTs (*Post-stimulus RTs > Implicit baseline* contrast)

	Cluster level				Peak level					
ROI	**P** FWE-corr	**P** FDR-corr	**K_E**	**P** unc	**P** FWE-corr	**P** FDR-corr	**T**	**P_{unc}**	**x,y,z {mm}**	**Gyral location (BA)** *(Left-L, Right-R)*
1	**0.000**	**0.000**	**2664**	**0.000**	**0.012**	**0.162**	**6.14**	**0.000**	**-6 -25 47**	**L-posterior cingulate (31)**
					0.018	0.162	5.93	0.000	-36 -40 59	L-middle frontal (1)
					0.022	0.162	5.84	0.000	6 -10 50	R-superior frontal (24)
2	**0.000**	**0.000**	**823**	**0.000**	**0.031**	**0.162**	**5.70**	**0.000**	**15 -67 -4**	**R-lingual (18)**
					0.033	0.162	5.67	0.000	-6 -70 17	L-cuneus (17)
					0.058	0.165	5.42	0.000	15 -61 14	R-cuneus (18)
3	**0.004**	**0.016**	**139**	**0.001**	**0.137**	**0.184**	**5.02**	**0.000**	**-48 -22 17**	**L-supramarginal (40)**
					0.222	0.211	4.78	0.000	-63 -16 11	L-inferior frontal (1)
					0.333	0.267	4.56	0.000	-45 -34 20	L-supramarginal (40)

Our conjunction analysis revealed a significant cluster of activation located in the primary visual cortex (peak voxel coordinate: X = -15, Y = -67, Z = -4) that was common to SPM maps of the *encoding* > *retrieval-old* contrast and *post-stimulus RTs* > *implicit baseline* contrast (see **Figure 2.6a**). Therefore, activation in this cluster was greater during encoding relative to retrieval-old and was also associated with longer post-stimulus RTs. **Table 2.6** outlines the local maxima for this cluster. Post-hoc brain-behaviour ROI correlations revealed a negative association approaching statistical significance between contrast estimates for this cluster and adjusted context recollection accuracy scores (r(28) = -.33, p = .078) (see **Figure 2.6 b**). The composite measure of EDU/IQ did not predict contrast estimates for this cluster across participant s (p > .05).

a)



b)

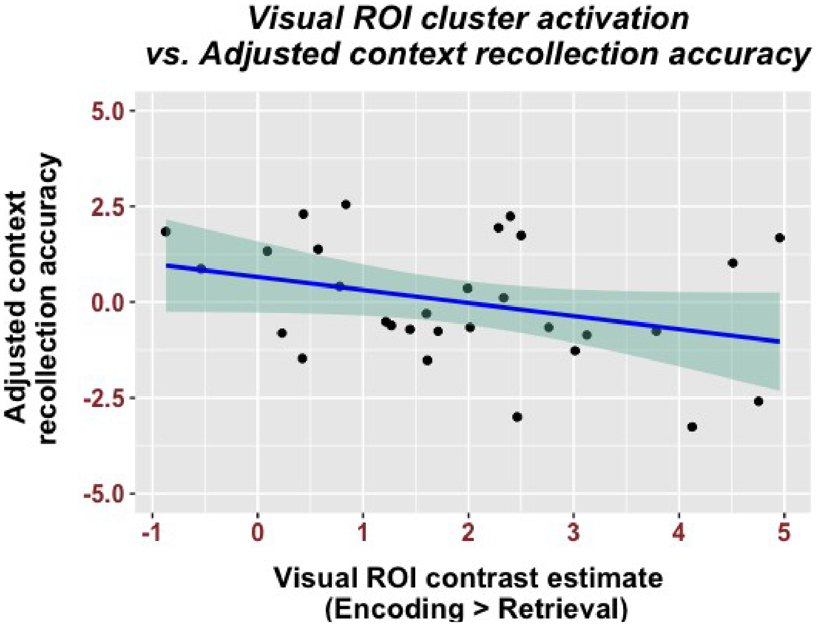


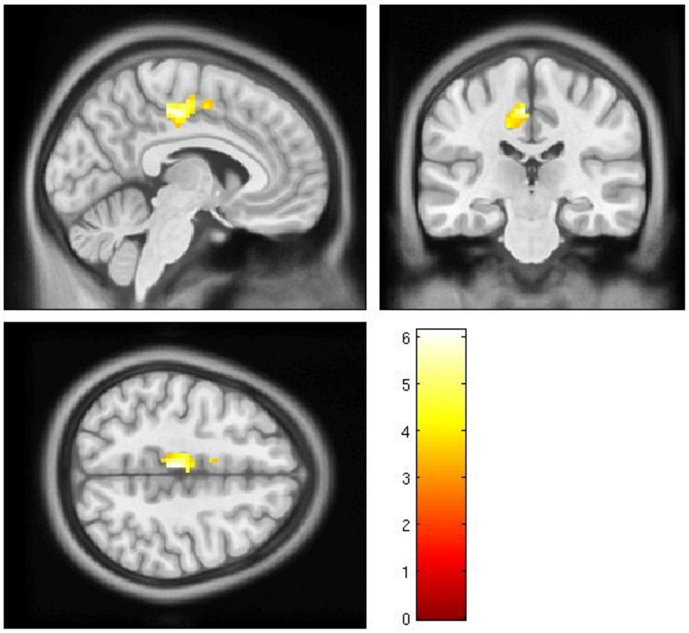
Figure 2.6 Primary visual cortex cluster as revealed by Encoding > Retrieval-old contrast that also showed higher activity with longer post-stimulus RTs

a) This SPM activation map shows a cluster of activation in primary visual cortex that was modulated by post-stimulus RTs such that longer post-stimulus RTs were associated with greater activation in this cluster at encoding. Results were formed by masking SPM map of post-stimulus RTs > baseline contrast by SPM map of encoding > retrieval-old contrast. b) A simple regression plot showing a negative association approaching statistical significance between contrast estimates for this cluster and adjusted context recollection accuracy scores.

Table 2.6 Brain regions showing higher activity with longer post-stimulus RTs (*Post-stimulus RTs* > *Implicit baseline* contrast) masked with Encoding > Retrieval-old contrast

	Cluster level				Peak level					
ROI	P FWE-corr	P FDR-corr	K_E	P unc	P FWE-corr	P FDR-corr	T	P_{unc}	x,y,z {mm}	Gyral location (BA) *(Left-L, Right-R)*
1	**0.000**	**0.016**	**595**	**0.001**	**0.031**	**0.162**	**4.63**	**0.000**	**-15 -67 -4**	**L-lingual (19)**
					0.033	0.162	4.61	0.000	-6 -70 17	L-cuneus (17)
					0.085	0.175	4.36	0.000	15 -61 -7	R-lingual (19)

For the conjunction analysis conducted to reveal clusters of activation common to the *implicit baseline* > *encoding,* and *post-stimulus RTs* > *implicit baseline* contrasts, a single cluster of activation (see **Figure 2.7a** and **Table 2.7**) was observed in the superior frontal gyrus (peak voxel coordinate: X = -6, Y = -25, Z = 47). This cluster showed task-induced deactivation at encoding (relative to baseline), however, activation in this cluster increased with longer post-stimulus RTs. Furthermore, post-hoc brain-behaviour ROI correlations revealed a significant positive association between contrast estimates for this cluster and adjusted context recollection accuracy scores (r(28) = .46, p = .037) (see **Figure 2.7b**). Therefore, task-induced deactivation in this cluster at encoding was associated with better context recollection accuracy. The composite measure of EDU/IQ did not predict contrast estimates for this cluster across participants (p > .05). **a)**



b)

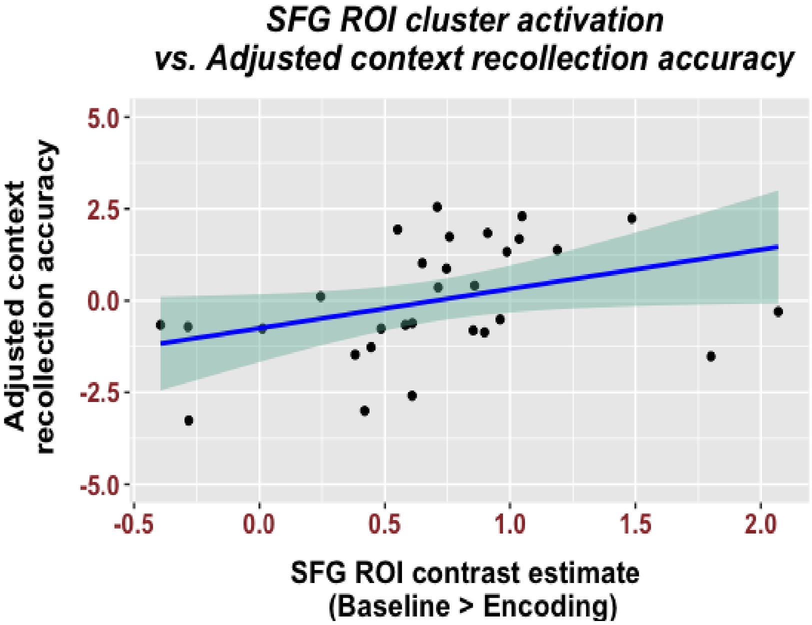


Figure 2.7 Superior frontal gyrus (SFG) cluster revealed by Baseline > Encoding contrast that showed less deactivation at encoding with longer post-stimulus RTs

a) This SPM activation map shows a cluster of activation in the SFG that was modulated by post-stimulus RTs such that longer post-stimulus RTs were associated with less deactivation in this cluster at encoding. Results were formed by masking SPM map of post-stimulus RTs > baseline contrast by SPM map of baseline > encoding contrast. b) A simple regression plot showing a significant positive association between contrast estimates for this cluster and adjusted context recollection accuracy scores

Table 2.7 Brain regions showing higher activity with longer post-stimulus RTs (*Post-stimulus RTs > Implicit baseline* contrast) masked with *Baseline > Encoding* contrast.

	Cluster level				Peak level					
ROI	**P** FWE-corr	**P** FDR-corr	**K_E**	**P** unc	**P** FWE-corr	**P** FDR-corr	**T**	**P unc**	**x,y,z {mm}**	**Gyral location (BA)** *(Left-L, Right-R)*
1	**0.003**	**0.016**	**146**	**0.001**	**0.012**	**0.162**	**6.14**	**0.000**	**-6 -25 47**	**L-superior frontal (6)**
					0.167	0.203	4.92	0.000	-3 -16 50	L-superior frontal (6)
					0.426	0.333	4.42	0.000	-9 -4 50	L-superior frontal (6)

2.5 Discussion

In the current study, we designed a novel task (AET) to examine how moment-by-moment drifts in attention at memory encoding, may impact memory performance for items and their contextual details, and modulate underlying fMRI activity. Pre-stimulus attention levels at encoding were gauged via RT to a fixation cross presented prior to object stimuli to be encoded on a trial-by-trial basis. Conversely, variation in encoding attention during stimulus presentation was indexed via RT to a fixation cross following each object stimulus. Our behavioural results revealed that variation in attention during encoding events predicted context memory success more broadly, but did not differentially impact context vs. item memory success. Pre-stimulus attention was not related to subsequent memory performance. The fMRI findings showed that trial-by-trial variation in attention during encoding events (but not pre-stimulus attentional variation) modulated task-evoked fMRI activity at encoding. Specifically, momentary interruption in attention during encoding events (as indicated by relatively longer post-stimulus RTs) was associated with increased fMRI activity in primary visual cortex and superior frontal gyrus. We tackle these findings and their implications in more detail below.

2.5.1 Behavioural effects of variation in attention at encoding in AET

Contrary to dual-task, divided attention paradigms that require participants to concurrently and simultaneously encode items into memory while engaging in a secondary task, the AET employed in the current study required participants to sequentially respond to a variable fixation cross and encode objects along with their associative spatial context into memory. Hence, this task can be considered a task-switching paradigm whereby two sets of stimuli are presented sequentially without temporal overlap (Kiesel et al., 2010; Monsell, 2003). We recently employed a similar task in our laboratory in a different study without the task-switching component (i.e., participants only had to memorize the stimuli without having to respond to a variable fixation) in a sample of healthy young adults (Snytte et al., 2020), and memory performance was comparable to that of the current study. Therefore, despite the task-switching nature of the current paradigm, task-switching costs were minimal. Moreover, unlike SART, the AET task is not purely a task of vigilance/sustained attention. Switching between the encoding stimulus and responding to the fixation cross likely disrupts the vigil. However, error rates in the current task predicted lapses in attention as measured via the CFQ scale (Broadbent et al., 1982), and showed a marginal positive association with task unrelated interference or mind-wandering (Mervielde et al., 1999). Hence, our task is sensitive to the experience of everyday attentional lapses, and may also be sensitive to mind-wandering similar to SART (Robertson et al., 1997; Smallwood et al., 2004).

Previous studies have demonstrated that encoding attentional state prior to episodic events impacts subsequent memory for those events (deBettencourt et al., 2018; Markant et al., 2014). Moreover studies using divided attention paradigms have demonstrated that when attention is divided during encoding, memory for contextual details is differentially impaired relative to item memory, presumably due to the greater attentional demands required for context memory encoding (Troyer et al., 1999; Troyer & Craik, 2000). As such, we predicted that spontaneous drifts in levels of pre-stimulus attention and/or levels of attention during encoding events, would differentially impact context memory performance relative to item memory, however, our results failed to support this hypothesis. Our findings also revealed that pre-stimulus levels of attention do not impact successful associative context recollection more broadly. Taken together, variation in attention at encoding in the AET did not differentially impact context vs. item memory performance, and pre-stimulus variation in attention did not predict context memory performance. The lack of association between pre-stimulus RTs (or post-stimulus RTs) and associative context vs. item memory may indeed reflect the insensitivity of context memory encoding to drifts in attention. However, this lack of association is likely a reflection of limitations in our task design. Our sample consisted of healthy young adults who performed the task generally well, scoring well above chance level and selecting the correct associative context on more than half of the trials. Yet, by virtue of our task design, more correct associative context trials would result in fewer item memory trials, hence creating an unbalanced number of events between the two stimulus categories. Indeed, there were significantly more correct associative context trials relative to item memory trials, which may have reduced the power in our logistic regression analysis. It is also possible that participants were aware of their performance on the task, such that relatively longer pre-stimulus RTs may have signalled that their attention was drifting away from the task. Consequently, this may have triggered the re-direction of attentional resources to task-relevant information, offsetting the effects of momentary dips in pre-stimulus attention, thereby not compromising context memory encoding performance (Smallwood et al., 2006). While our results may seem to suggest that pre-stimulus attention levels do not impact context memory encoding performance when taken at face value, these findings should be taken with a grain of salt given our novel task design and the task limitations discussed above (please also see limitations and conclusion section below).

We also investigated whether RTs presented immediately after an object encoding event would predict associative context recollection more broadly. The variable fixation cross staggered between the object stimuli at encoding lasted 4 secs on average before expanding in size and a behavioural response was made. Therefore, RT to a fixation cross presented after an object stimulus potentially reflects the attentional state of a participant during that object presentation or moments after leading to the subsequent behavioural response. Our results revealed that post-stimulus RTs did in fact predict associative context memory encoding success more generally. That is, relatively slower post-stimulus RTs, presumably signalling brief interruptions in attention either during the encoding event itself or moments after predicted context memory failure, and relatively quicker post-stimulus RTs predicted context memory hits.

Overall, our findings suggest that there are attention states where individuals are optimally tuned in for successful context memory encoding and other states where contextual details are likely to be missed. One possible mediator of these effects is mind-wandering, or the shift of attention from task-related processes to self-generated processes unrelated to the task

(Smallwood & Schooler, 2006). In the current study, mind wandering, was only marginally related to error rates (p = .078) on the task and was not directly linked to memory performance. However, mind-wandering in the current study was assessed via a self-report questionnaire presented at the end of the study, and therefore may not have captured the moment-by-moment variation in attention that occurred during the encoding task. Furthermore, evidence linking mind-wandering to task performance is inconsistent throughout the literature (McVay & Kane, 2012; Seli et al., 2015). Task-unrelated thoughts (i.e., mind-wandering) could also be assessed via thought probes presented on a trial-by-trial basis (Seli, Risko, & Smilek, 2016; Seli et al., 2018), however, we opted against this method since it would add another level of task-switching to our paradigm , making it difficult to conclude whether attention or task-switching demands mediated task performance. According to mind-wandering theory, task-unrelated thoughts stem from underload, or underarousal associated with a task (Robertson et al., 1997; Seli, Risko, Smilek, et al., 2016; Thomson et al., 2014). Given the high memory performance level on the current task and its low level of complexity, we speculate that our task afforded most participants to disengage their attention from context memory encoding to task unrelated thoughts (i.e., mind-wandering) on some trials, thus interrupting encoding operations such binding an event's content to its source that are required for successful context memory performance (Zimmer et al., 2006). This may explain the positive relationship between slower post-stimulus RTs at encoding and context memory failure.

Although most participants in the current study demonstrated a positive relationship between slower post-stimulus RTs at encoding and context memory failure, a few participants demonstrated the opposite pattern of results (i.e., slower post-stimulus RTs linked to context memory success). One possible explanation is that these participants could potentially be demonstrating speed-accuracy trade-offs. That is, rather than giving equal weight to responding to the fixation cross and encoding a given stimulus, they could be directing more cognitive resources towards the encoding task by rehearsing the object stimuli during the presentation of the fixation cross, thereby responding relatively slowly to the fixation stimuli. However, this strategy may not be beneficial to performance since participants showing a positive relationship between faster post-stimulus RTs and associative context memory success showed more accurate associative context memory performance compared to those who demonstrated the opposite pattern.

2.5.2 The effect of variation in attention on encoding-related functional activity in the AET

Prior to investigating the effects of RT modulation on fMRI activity at encoding, we first identified task-related regions that were generally more active during encoding relative to the retrieval of object stimuli during the AET. Prominent regions identified include bilateral primary visual (BA 17) and lateral occipital cortices (BA 18/19), left superior (BA 8/9) and inferior frontal (BA 45/47) gyri, and lateral temporal cortex. Our findings are consistent with previous accounts implicating these regions in episodic encoding in young adults (Cansino et al., 2002; Kim, 2011; Mitchell & Johnson, 2009; Spaniol et al., 2009). The lateral occipital regions identified in this particular contrast overlap with an area that has been coined the 'lateral occipital complex', which is thought to play a key role in visual object recognition (Grill-Spector et al., 2001; Malach et al., 1995). Furthermore, recruitment of visual association cortex during memory encoding of visual stimuli has been linked to successful subsequent memory (Grill-Spector et al., 2001; Hasinski & Sederberg, 2016; Xue et al., 2010). On the other hand, the frontal and lateral temporal lateral temporal regions identified have been previously hypothesized to play a role in conceptual (semantic) processing of items (Badre & Wagner, 2007; Gabrieli et al., 1998; Lambon Ralph, 2014; Patterson et al., 2007). Our analysis also identified a core set of regions that displayed task-induced deactivation during encoding relative to baseline. These include the midline frontal regions, PCC, lateral parietal areas, bilateral insula, and superior frontal regions (BA6). Results from our spatial correspondence 'spin-test' indicated a significant spatial correspondence between the contrast image showing task-induced deactivation and each of the DMN, sensorimotor, and salience canonical functional networks as defined by the Yeo Atlas (Yeo et al., 2011). Indeed, the midline frontal, PCC, and lateral parietal areas identified overlap considerably with the DMN, which is consistently comprised of the PCC, medial frontal cortex, as well as left and right lateral parietal cortices (Buckner et al., 2008; Raichle et al., 2001). On the other hand, the insula is considered a key node in the salience network and is thought to coordinate the brain's response for detecting behaviourally relevant stimuli (Uddin, 2015). Finally, areas in the superior frontal gyrus identified are part of the sensorimotor network, commonly implicated in tasks requiring a motor response (Yeo et al., 2011; Uddin et al., 2019). The implicit baseline condition that was compared against the encoding condition to form the encoding-related deactivation contrast (i.e., *implicit baseline > encoding*) included the ITI during which participants had to respond to the expanding fixation cross. Therefore, the aforementioned regions were less active during the encoding condition relative to the expanding fixations, or more active during the expanding fixation condition relative to the encoding condition. As such, it is not surprising to see engagement of sensorimotor and salience network regions in this contrast. More importantly, this contrast was initially used to identify DMN regions that were less active during encoding relative to baseline.

Our main question of investigation revolved around whether pre-stimulus and post-stimulus RTs modulated task-induced activations and DMN deactivations at encoding.

Relatively longer post-stimulus RTs on a trial-by-trial basis signalling momentary slips in attention during encoding presentations were associated with higher activity in primary visual cortex and reduced deactivation in SFG. Although there were theoretical reasons to expect attenuations in encoding-induced activity related to momentary interruptions in attention at encoding, and less deactivation of DMN regions (as outlined in the introduction section), we did not observe these findings. The current sample consisted of healthy young adults that performed the task well above chance level signalling that they were generally attentive. Yet, it is possible that there were additional subtle modulations in fMRI activity related to variation in attention at encoding that were not captured by our RT measure and/or parametric modulation analysis. Nonetheless, our current results suggest that variation in attention during encoding events as indexed by post-stimulus RT, exhibited significant modulations in task-related activation and deactivation.

Taken at face value, our finding that momentary interrution in attention during encoding events was associated with greater primary visual cortex activation may seem at odds with the notion that attention enhances sensory cortical activity to bias the binding of contextual information into memory (Uncapher & Rugg, 2009). Traditional feature-detection models of visual perception posit that visual features of an item are extracted in a largely sequential, feed-forward manner, with minimal influence from higher areas to lower areas (Fukushima, 1980; Mel, 1997). Therefore, according to these models, enhanced sensory representations of a visual item ostensibly mediated by attention, would be expected to manifest as higher cortical activity in the visual cortex. However, evidence based on probabilistic models have proposed a dissociation in visual cortex such that higher order visual regions may suppress neural responses in primary visual regions that are consistent with current high level expectations through feedback mechanisms (Mumford, 1992; Murray et al., 2002; Rao & Ballard, 1999). For example, Murray and colleagues (2002) used fMRI to measure cortical responses in LOC and primary visual cortex to visual elements that were either grouped together as objects or were randomly arranged. The authors observed greater activity in LOC combined with reduced primary visual cortex activity in response to elements that formed coherent shapes. This suggests that activity in early visual regions is suppressed via grouping processes performed in higher areas. It is important to note that it is not grouping per se that leads to reduced activity in primary visual cortex, but the degree to which neurons in higher level visual regions are tuned for the contextual features of a stimulus (Murray et al., 2002). To investigate how these activity reductions in primary visual areas were related to sensory representations, Kok et al., (2012) used fMRI and multivariate pattern analysis (MVPA) techniques to measure neural activity and representational content in the visual cortex where expectations about visual stimuli were manipulated. Findings revealed that perceptual expectation reduced activity in primary visual cortex, but improved the stimulus representation in this area. Therefore, this implies that stimulus expectation supports perception by sharpening sensory representations. In the context of our findings, our data suggests that reductions in primary visual cortical activity with shorter post-stimulus RTs (i.e., enhanced attention during encoding events), possibly mediated by higher order visual areas may signal stronger sensory representations of object stimuli (and their location) to support associative encoding. In contrast, momentary slips in attention during encoding events may weaken these representations as evidenced by greater activity in primary visual cortex. Although speculative, our data shows that longer post-stimulus RTs (signalling brief interruptions in attention during encoding events) in addition to being associated with increases in primary visual cortex activity, were also concurrently associated with decreases in bilateral LOC activity (p <

.001 uncorrected) (see supplementary **Figure 2.8** and **Table 2.8**). Despite that the LOC regions in association with post-stimulus RTs did not survive our stringent cluster-based FDR threshold, these findings lend further support to our interpretation that trial-by-trial variation in levels of attention during encoding events modulate activity in the visual cortex, potentially impacting the contextual representations of encoded items. This also compliments more general evidence that modulation of visual cortical representation areas by attention at encoding is important for later remembering (Long et al., 2018; Prince et al., 2009).

In addition to modulations in visual cortical activity by post-stimulus RT at encoding, our findings revealed that longer post-stimulus RT on a trial-by-trial basis was associated with less deactivation in SFG at encoding. This cluster (peak: -6 -25 47: see figure 5) lies within the premotor/supplementary motor area, and is part of the sensorimotor network identified in the encoding-deactivation contrast (*implicit baseline* > *encoding*). More deactivation in this cluster during encoding was also associated with better subsequent context memory performance at the between-participant level. Emerging evidence suggests that in memory studies that combine stimulus encoding with button pressing, motor-related operations may interfere and compete with encoding processes, thereby impairing subsequent memory performance. For example, in a study that combined fMRI with a go/no-go task, followed by a surprise recognition memory for go/no-go cues, Chiu and Egner (2015b) found that memory was worse for no-go than for go stimuli. Furthermore, they found that brain regions associated with response inhibition, including the supplementary motor area, were relatively more active during the encoding of subsequently forgotten than remembered no-go cues, implying that cognitive operations related to motor processing such as response inhibition temporarily reduces attentional resources available for successful stimulus encoding. During the presentation of the expanding fixation and execution of the motor responses in the AET, activity in the identified SFG cluster was greater relative to the encoding events. Given the nature of the AET task, which requires participants to sequentially provide a motor response to the expanding fixations and encode object-location associations into memory, it is possible that motor-related operations may have interfered and competed with memory encoding processes and that this pattern of results reflect the motor demands of the task. This interpretation is inline with the common resource hypothesis, which posits that inhibitory control processes related to the execution of motor responses at encoding, may sap away attentional resources from mnemonic stimulus encoding thereby hindering subsequent memory performance (Chiu & Egner, 2015a, 2015b).

2.5.3 Limitations and conclusion

Three limitations of this study are salient. First, the absence of any significant modulations in encoding fMRI activity or subsequent memory performance by the state of pre-stimulus attention may reflect a limitation in the AET task design. Pre-stimulus attention was gauged via button pressing in response to an expanding fixation prior to the encoding event. However, there were two seconds unaccounted for which was the duration between the pre-stimulus expanding fixation and the appearance of the ensuing encoding event. Therefore, pre-stimulus RT may not have adequately captured the moment-by-moment drifts in attention prior to an encoding event. This is likely given the wealth of evidence suggesting a link between pre-stimulus brain state and memory performance (Fernandez et al., 1999; Guderian et al., 2009; Otten et al., 2006; Turk-Browne et al., 2006; Yoo et al., 2012). Second, the current study does not allow us to infer the content of thought during drifts of attention at encoding. Upon completion of the task, participants were asked to complete the thinking content component of the DSSQ (Mervielde et al., 1999) to assess the content of thought during the task. However, this precludes from investigating the content of thought on a trial-by-trial basis as they pertain to RT variations and modulations in encoding activity. Third, the attentional state during encoding events was inferred via button pressing in response to an expanding fixation that ensued encoding events. Therefore, post-stimulus RT may have captured the state of attention during the encoding event leading up to the behavioural response, but it is difficult to ascertain the exact timing and duration of these momentary drifts in attention. Perhaps combining the AET task with EEG or eye tracking may shed light on the temporal effects of trial-by-trial variation in attention as they pertain to associative memory.

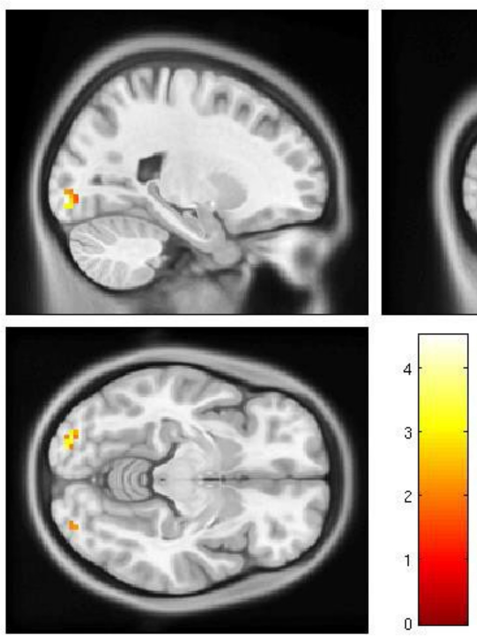
In sum, our study introduces a novel paradigm to investigate the influence of the ebb and flow of attention at encoding on memory performance and underlying fMRI activity. Our behavioural findings reveal that context memory success is related to an efficient state of attention during encoding. In addition, momentary interruptions in attention at encoding were associated with enhanced activity in primary visual cortex that may reflect poor sensory representations of object-location associations. Brief slips in attention during encoding events were also associated with less deactivation of premotor/supplementary motor regions, which may reflect inefficient allocation of attentional resources towards encoding-related processes. Teasing apart the specific cognitive and neural operations related to variation in attention that contribute successfully to context memory encoding is worth investigating in future studies to expand the literature on the interaction between the attention and memory systems. Furthermore, understanding the factors related to individual differences in the relationship between drifts in attention and memory performance would shed light on the susceptibility of individuals to memory failures, and may offer a unique window for investigating the optimal conditions required for learning and memory.

2.6 Acknowledgements

No part of the study procedures or analysis was preregistered in an institutional registry prior to the research being conducted. 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. However, the scripts used to conduct analysis will be made available on Open Science Framework. This work was supported by Natural Science and Engineering Council of Canada (NSERC) # 8400826 awarded to M. N. Rajah. We thank the participants of our study for their time and support in making this project possible.

2.7 Supplementary

Supplementary Figure 2.8 Peaks in lateral occipital cortex that showed lower activation with longer post-stimulus RTs



Supplementary Table 2.8 Brain regions showing lower activity with longer post-stimulus RTs *(Implicit baseline contrast > Post-stimulus RTs)*

	Cluster level				Peak level					
ROI	P FWE-corr	P FDR-corr	K_E	P unc	P FWE-corr	P FDR-corr	T	P unc	x,y,z {mm}	Gyral location (BA) *(Left-L, Right-R)*
1	1	0.831	31	0.575	0.364	0.035	4.51	0.000	-24 -94 -7	L-lingual (18)
2	1	0.831	6	0.831	1	0.563	2.36	0.013	30 -91 -7	R-lingual (18)

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Chapter 3. Study 2: The association between cognitive reserve and performance-related brain activity during episodic encoding and retrieval across the adult lifespan

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Preface

The primary goal of this thesis was to investigate whether educational attainment and crystallized IQ contribute to individual differences in the behavioural and neural effects of levels of attention at encoding and aging on context memory. As mentioned in the general introduction section, the majority of studies assessing the contribution of educational attainment and crystallized IQ to individual differences in episodic memory have done so within the context of aging. However, these factors are presumed to allow individuals to circumvent memory failures by utilizing alternate neurocognitive strategies in the face of task demands, and thus may not be necessarily dependent on age.

In study 1, we explored whether levels of education and crystallized IQ may contribute to individual differences in context memory by influencing the relationship between momentary drifts in attention at encoding and subsequent memory performance, as well as underlying fMRI activity in sample of younger adults. We created the AET task, which is a hybrid task of spatial context memory and attention, and we focused our fMRI analysis on the encoding phase. This was done given that the effects of attention on context memory are more pronounced at encoding

(Craik et al., 1996; Naveh-Benjamin et al., 1998; Naveh-Benjamin et al., 2006), especially when spatial location is used as the context memory task (Troyer et al., 1999; Troyer & Craik, 2000).

In study 2, we extended our investigation of individual differences in context memory by specifically focusing on age-related effects. We used a task paradigm that consisted of spatial and temporal context memory encoding and retrieval phases at different levels of task difficulty. Data from a large adult life-span sample (n = 154) that included younger, middle-aged, and older adults were analyzed using multivariate Behaviour Partial Least Squares (B-PLS). Treating age as a continuous variable, we assessed task-related, whole-brain patterns of activity that correlated with age, education and crystallized IQ, and task performance. As an exploratory analysis, we also assessed whether education and crystallized IQ moderates the relationship between cortical thickness and age. These analyses allowed us to examine whether education and crystallize IQ contribute to individual differences in context memory aging and the neural mechanisms that may underlie these differences.

3.1. 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.

3.2 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.

3.3 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.

3.3.1 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.

3.3.2 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 3.1**).

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).

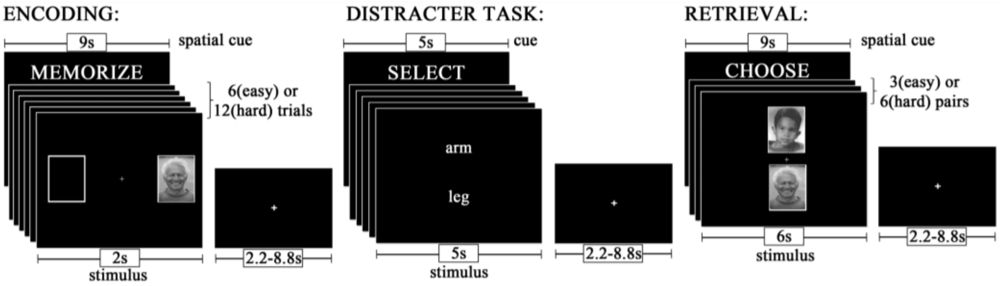


Figure 3.1 Timeline of fMRI task procedure

3.3.3 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.

3.3.4 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).

3.3.5 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)

3.3.6 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 ~ □□+ Age + Reserve + Age*Reserve + □, 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)

3.3.7 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.

3.3.8 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).

3.3.9 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.

3.4 Results

3.4.1 Behavioural results

Table 3.1 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 ($F(2,151) = 7.79$, $p < 0.001$, $\eta 2 = 0.094$).

3.4.2 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, $p < 0.001$, η2 = 0.228), task (F (1, 150) = 618.90, $p < 0.001$, η2 = 0.805), difficulty (F (1, 150) = 107.06, $p < 0.001$, η2 = 0.416), and a task x difficulty interaction (F (1, 150) = 32.35, $p < 0.001$, η2 = 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.

3.4.2 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, $p < 0.001$, η2 = 0.147), task (F (1, 150) = 154.83, $p < 0.05$, η2 = 0.508), and difficulty (F (1, 150) = 29.05, $p < 0.05$, η2 = 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).

Table 3.1. 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	2501	2781
	(78.60)	(63.12)	(71.20)
Temporal easy retrieval	2596	2966	3157
	(84.51)	(59.94)	(88.97)
Spatial hard retrieval	2303	2628	2837
	(74.03)	(54.12)	(77.34)
Temporal hard retrieval	2777	3099	3185
	(95.58)	(75.70)	(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 (η2) 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.

3.4.3 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.

3.4.4 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 3.2. Figure 3.2a** 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 3.2**).

Table 3.2: 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).

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 3.2c** and **3.2d** respectively. Local maxima denoting positive and negative saliences for this LV are presented in **Table 3.3**. 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.

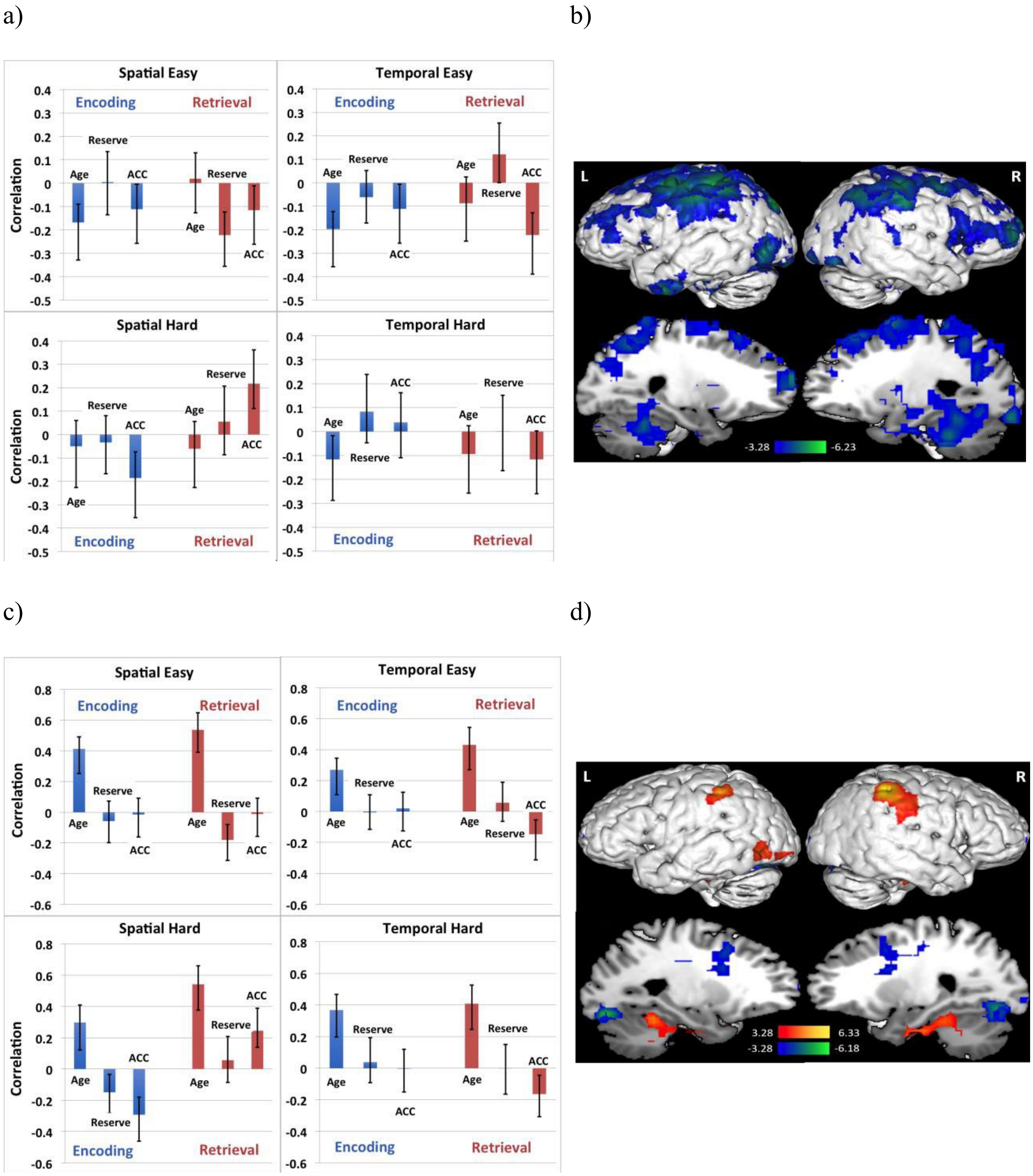


Figure 3.2 Brain-behaviour correlation profiles and corresponding singular images for LV1 and LV2

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)).

Table 3.3: 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

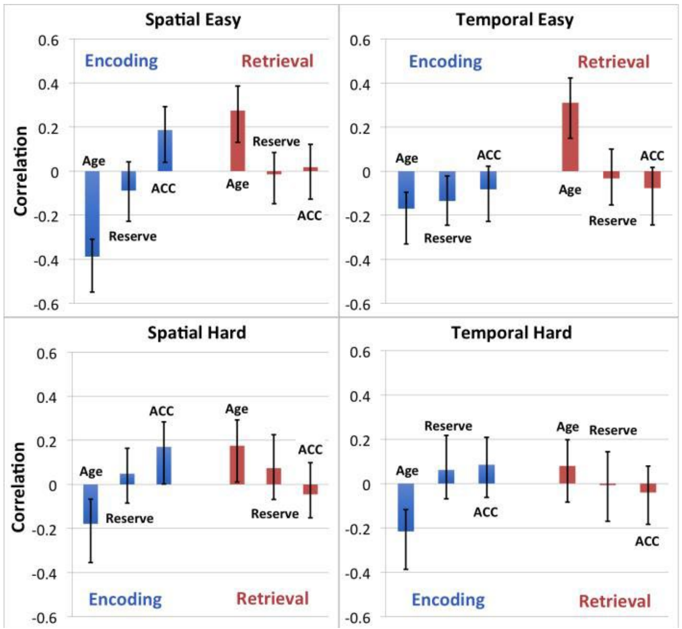
	3	4.15	53	-2	-18	57	Medial frontal	6
Right								
	2,3	6.33	140	54	-39	41	Inferior parietal	40
	4	5.06	678	18	-18	-22	Parahippocampal	28
	4	4.89	33	6	34	62	Superior frontal	6
	4	4.39	24	37	16	-30	Superior temporal	38

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).

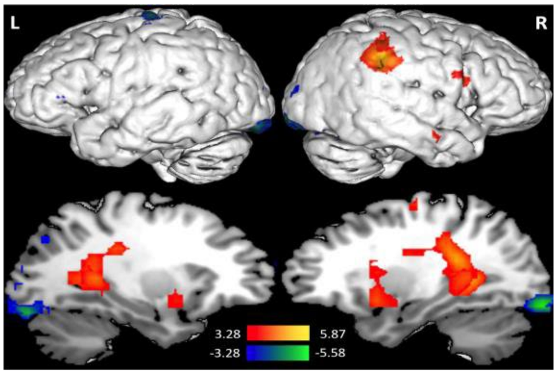
LV3 accounted for 9.52% of the total cross-block covariance ($p < 0.001$). This LV identified brain regions that were differentially related to age during encoding and retrieval (age x phase effect). The local maxima of positive and negative voxel saliences are presented in **Table 3.4.** The PLS correlation profile and the corresponding singular image for LV3 are presented in **Figures 3.3a** and **3.3b** respectively. Based on the PLS correlation profile, activity in positive salience brain regions (warm coloured regions in **Figures 3.3b**) 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 3.3b**) 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 3.5**. Based on the PLS correlation profile (**Figure 3.3c**) and the corresponding singular image (**Figure 3.3d**), 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.

a)



b)



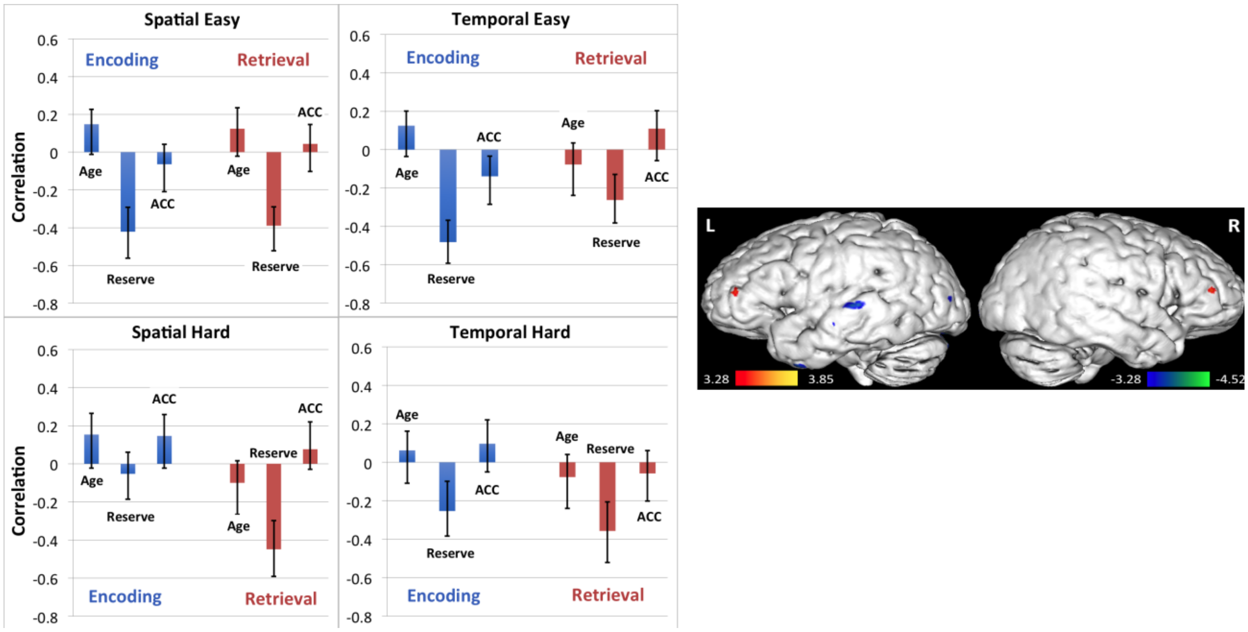

c) d)

Figure 3.3 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/).

Table 3.4: 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 3.5: 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).

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.

3.4.5 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 3.4**. 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.

3.5 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.

3.5.1 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 ($F(2,151) = 6.88$, $p < 0.001$, $\eta2 = 0.083$), and temporal easy ($F(2,151) = 11.87$, $p < 0.001$, $\eta2 = 0.136$) 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).

3.5.2 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).

3.5.3 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.

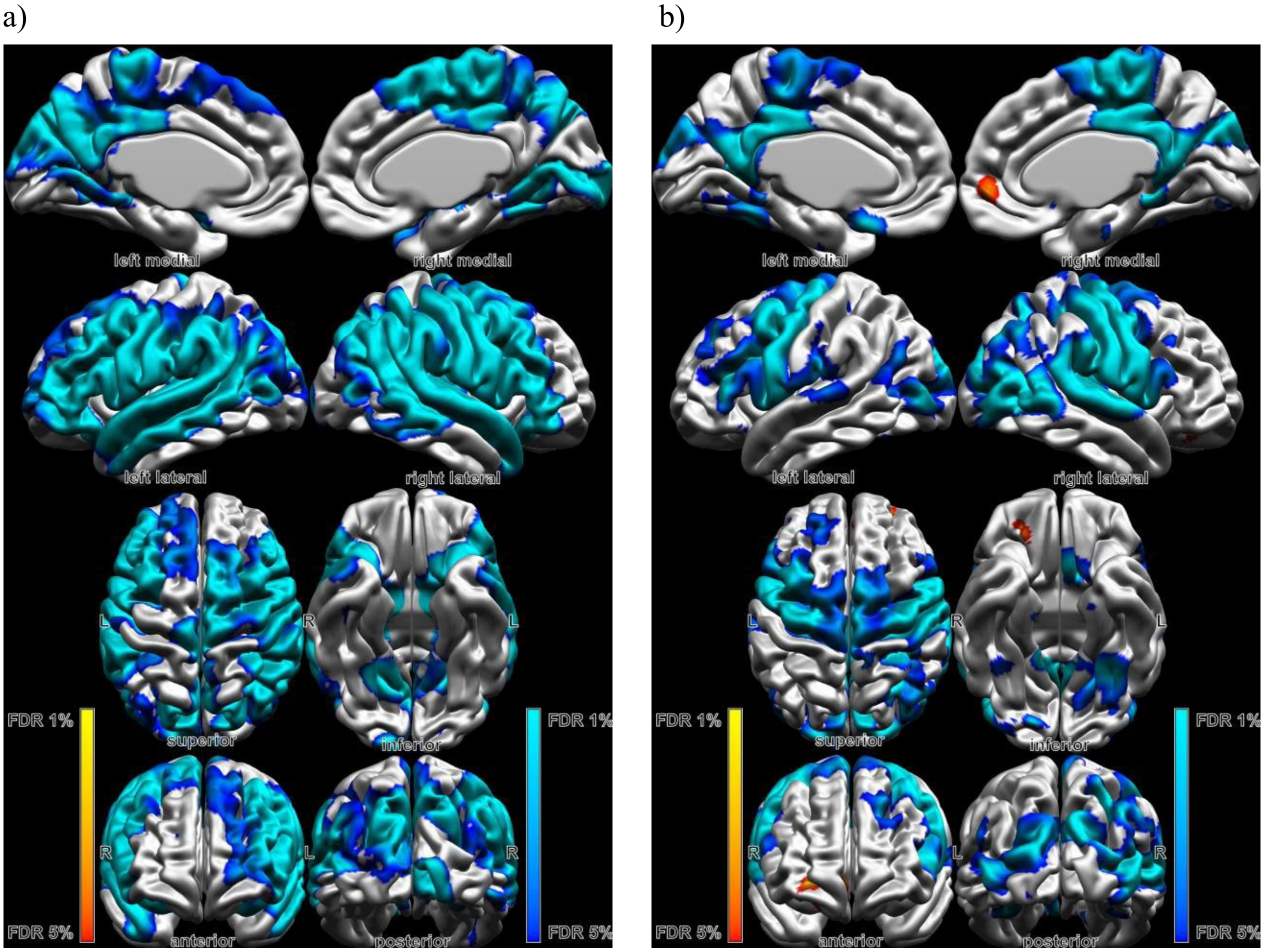
3.6 Acknowledgements

No part of the study procedures or analyses was preregistered in an institutional registry prior to the research being conducted. This work was supported by Canadian Institute of Health Sciences (CIHR) Operating Grant #MOP126105 funded to M. N. Rajah and Natural Science and Engineering Council of Canada (NSERC) RGPIN-2018-05761 awarded to M. N. Rajah. We thank the participants of our study for their time and support in making this project possible.

3.7. Supplementary material

3.7.1 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 3.4 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.

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Chapter 4. General Discussion

The overarching objective of this thesis was to investigate whether educational attainment and crystallized intelligence account for some of the inter-individual variability in the behavioural and neural effects of factors known to affect context memory in healthy adults, namely levels of attention at encoding and advanced age. As alluded to in the introduction, there are many factors that can impact context memory in healthy individuals, but encoding under conditions of compromised attention (e.g., divided attention) and aging are known to selectively impair context memory. Levels of educational attainment and crystallized intelligence have often been proposed as mediators of inter-individual differences in memory performance. Historically, educational attainment and crystallized intelligence have been studied within the context of aging and cognitive reserve. These factors have been hypothesized to contribute to an individual's *reserve,* or accumulated neurocognitive resources, which presumably soften the impact of age-related changes on episodic memory. Generally speaking, educational attainment and crystallized intelligence are thought to reflect accumulated knowledge and cognitive strategies, which may grant individuals the capability to process memory tasks in ways that render them less susceptible to memory failures. In this thesis, we examined whether, and how educational attainment and crystallized intelligence may contribute to individual differences in the effects of encoding attention (Study 1) and advanced age (Study 2) on context memory performance and functional brain activity.

In study 1, we examined whether educational attainment and crystallized IQ contribute to inter-individual variability in the effects of encoding attention on context memory performance and related fMRI activity. To that end, we developed a novel and innovative event-related fMRI task paradigm and called it the Attention at Encoding Task (AET). Our main findings indicated that the ebb and flow of attention during encoding events impact subsequent retrieval of associative context memory. Furthermore, we found that momentary interruption in attention at encoding was associated with enhanced activity in primary visual cortex and less deactivation of premotor/supplementary motor regions, possibly reflecting inefficient allocation of attentional resources towards associative encoding-related processes. More importantly, educational attainment and crystallized IQ did not account for inter-individual variability in these attentional effects on context memory performance or fMRI activity. Due to the COVID-19 pandemic and subsequent halting of human subject testing at our facilities, we lacked an older adults sample and couldn't concurrently examine whether educational attainment and crystallized IQ account for inter-individual variability in the effects of advanced age on context memory performance and fMRI activity. In study 2, we extended our findings by reanalyzing data from a large adult lifespan sample consisting of younger, middle-aged, and older adults. We used data-driven multivariate B-PLS analysis to assess whether educational attainment and crystallized IQ (referred to as cognitive reserve in study 2) modulate age-related effects of context memory performance and fMRI activity at encoding and retrieval. We found that advanced age was associated with enhanced anterior and lateral frontal, inferior parietal, medial temporal, and occipito-temporal activity at encoding, which may reflect age-related functional compensation. Yet, this compensatory pattern was not associated with years of educational attainment or crystallized IQ. Our exploratory analysis also indicated that educational attainment and crystallized IQ did not explain age-related effects on cortical thickness. Therefore, converging evidence across studies indicate that years of educational attainment and crystallized IQ do not account for individual differences in the effects of attention during encoding or age on context memory performance, fMRI activity, or cortical thickness.

4.1 Effects of attention at encoding and advanced age on context memory are not mutually exclusive

We will discuss the null effects related to years of educational attainment and crystallized IQ in the paragraphs below, however, it is important to note that the effects of attention during encoding and aging on context memory are not mutually exclusive. As outlined in the introduction, successful context memory relies on the allocation of attentional resources towards perceptual and reflective processing, and context memory encoding in particular is an effortful process that hinges on the flexible engagement of attention (Troyer et al., 1999; Troyer & Craik, 2000). According to the *attentional resources theory* (Craik & Byrd, 1982), advanced age is associated with declines in attentional resources, which impact cognitive tasks requiring the most effort. Therefore, age-related declines in context memory are partially mediated by declines in attentional resources with age. LV1 in study 2 showed that during encoding, context memory success with advanced age was associated with an upregulation of brain regions implicated in attention (e.g., lateral PFC and inferior parietal regions), as well as posterior occipito-temporal regions associated with visual processing. This pattern represents a form of functional compensation to maintain task performance in the face of age-related changes. Interestingly, the encoding-related occipital visual regions in LV1 of study 2 overlap with the occipital regions in study 1 related to visual processing that are modulated by variations in attention at encoding. This suggests that age-related effects on context memory are not independent from the effects related to attention at encoding. However, the effects related to attention during encoding maybe independent of age-related effects since study 1 examining those attentional effects consisted of a sample of young adults only. We had planned to recruit a sample of older adults and test them on the AET task to further examine the interaction between attention and age effects on context memory performance and fMRI activity, however, the shutdown of MRI subject testing at the Brain Imaging Centre at the Douglas Mental Health Institute due to the COVID-19 pandemic interrupted those plans. Given our converging findings from studies 1 and 2, we predict stronger associations between attention at encoding, and context memory performance as well as underlying fMRI activity in older adults performing the AET. However, we do not expect educational attainment or crystallized IQ to modulate those effects.

4.2 Null effects related to educational attainment and crystallized intelligence

Across studies 1 and 2, we conclude that levels of educational attainment and crystallized IQ do not mediate individual differences in the effects of encoding attention or aging on context memory performance or fMRI activity. We utilized the same composite measure in both studies, which consisted of an average of years of educational attainment and crystallized IQ based on the AMNART scale. These null findings may potentially reflect the high level of education in our study 1 (mean EDU = 15.80 yrs, EDU range = 12 – 20 yrs) and study 2 (mean EDU = 15.60 yrs, EDU range = 11 – 20 yrs) samples. Previous studies showing an association between years of education and episodic memory (e.g., Angel et al., 2010) included samples with lower levels of education, therefore, it is possible that higher levels of education may have diminishing marginal effects on cognitive performance, and thus may be difficult to capture in samples of highly educated individuals (Lövdén et al., 2020). Nonetheless, LV4 in study 2 revealed an age-invariant pattern of brain activity that was related to education and crystallized IQ (albeit not related to task performance). This implies that the null effects observed may not be related to restricted range or ceiling effects. Alternatively, it is possible that years of educational attainment and crystallized IQ, which correlated with activity in brain regions important for semantic memory (LV4 in study 2) did not adequately capture the cognitive processes important for context memory. Both the AET task in study 1 using object stimuli, and the context memory task in study 2 using face stimuli strongly modulated posterior brain regions important for visual processing. It is possible that using a measure that reflects one's experience with the particular category of stimuli in a given context memory task, an association between that measure, context memory performance, and underlying brain activity may then be observed. In case of face stimuli for instance, this could be a measure reflecting social engagement or extraversion (e.g., Conroy et al., 2010; Pichet Binette et al., 2020).

Studies assessing the role of educational attainment on episodic memory performance have provided conflicting evidence with some showing strong associations (e.g., Angel et al., 2010; Lee et al., 2012), while others showing no statistically significant associations (e.g., Zahodne et al., 2011). Moreover, educational attainment has been assessed differently in different studies. For instance, indices include years of formal education (Berggren et al., 2018; O'Shea et al., 2018; Zahodne et al., 2011) similar to our methods in studies 1 and 2; levels of education stratified into multiple groups ranging from no formal education to an undergraduate degree and above (Bertola et al., 2019; Williams et al., 2021); and categories yielded by dichotomizing education into lower and higher levels (Angel et al., 2010). A major challenge with employing self-reported years of education as a measure of educational attainment is that this method does not account for cohort differences in the content of education, which may differ across age, cultural, and social groups. Indeed it has been suggested that literacy may be a better indicator of educational attainment than years of formal education (Manly et al., 2003, 2005). However, assessing literacy presents its own set of challenges as it may be influenced by factors such as learning difficulties. Due to the relative ease of obtaining details about educational level, measures based on years of education are still used, and in the context of aging, years of formal education is one of the most common proxy measure of cognitive reserve (Tucker & Stern, 2011).

As evidenced in this thesis, educational attainment and crystallized IQ do no explain individual differences in the effects of encoding attention and aging on context memory performance and functional brain activity. These null effects may potentially reflect the high level of education in our samples, the possibility that the composite measure used did not adequately capture the cognitive processes important for context memory, or differences in the way that educational attainment was assessed in different studies. We chose years of educational attainment and crystallized IQ to assess individual differences in context memory given the assumption that these measures represent accumulated knowledge, cognitive strategies, and a host of other lifestyle and socio-contextual factors that may benefit episodic memory (Stern et al., 2018; Tucker & Stern, 2011). Yet, it is doubtful whether the measures employed are sufficient in capturing the diverse experiences and exposures that contribute to the development of effective cognitive strategies. More recent investigations have utilized more comprehensive measures of life exposures such as the Lifetime of Experiences Questionnaire (Valenzuela & Sachdev, 2007) and the Cognitive Reserve Index Questionnaire (Nucci et al., 2012) (e.g., Borgeest et al., 2020; Mendoza-Holgado et al., 2021; Quattropani et al., 2021).

4.3 Limitations

Several limitations of these studies are apparent. Firstly, due to the lack of an older adults sample in study 1, it was impossible to examine the interaction between the effects related to variation in attention during encoding, aging, and how these effects maybe modulated by educational attainment and crystallized IQ. As discussed above, the effects related to encoding attention and aging are intertwined, and so our findings only represent one piece of a larger puzzle. Testing a sample of older adults on the AET may allow for a more direct assessment of attentional and aging effects on context memory, their interaction, and whether education and crystallized IQ mediate inter-individual variability in these effects.

Secondly, our task designs of studies 1 and 2 are not without their shortcomings. We have discussed limitations in the design of the AET in detail (please refer to section **2.5.3**). In brief, a) pre-stimulus RT may not have adequately captured variation in attention prior to an encoding event since there exists a duration of two seconds that is unaccounted for; b) the AET does not allow us to infer the content of thought during variation of attention at encoding; c) Variation in attention were inferred via button pressing and this may have captured the state of attention leading up to the behavioural response, but it is difficult to ascertain the exact timing and duration of these momentary drifts in attention using response times only. With regards to the context memory task in study 2, we only investigated effects on fMRI activity during correct trials given the insufficient number of incorrect trials in our data. In addition to reductions in true memories, age-related declines in episodic memory are also characterized by a greater likelihood of falsely remembering or misattributing erroneous details of past events (Schacter et al., 1997), due to the reliance on self-referential or general semantic information in old age (Mather et al., 1999). A more comprehensive examination of age-related effects in context memory would thus benefit from assessing age-related functional activation patterns related to successful vs. unsuccessful context memory (i.e., context misattribution and context forgetting) across the adult lifespan.

4.4 Future directions

The studies enclosed have naturally incited a number of additional lines of inquiry. For example, to what extent are context memory declines in old age mediated by variations in attention at encoding? Do the effects of aging and variations in attention at encoding on context memory share common neurocognitive mechanisms? Memory and attention have often been investigated separately despite their well established bidirectional interactions (Hannula, 2018; Long et al., 2018). While this tradition has led to critical domain-specific findings, they remain limited in scope. Questions regarding when and how attention and memory interact, the neural mechanisms that support those interactions, and their effect on behaviour remain relatively underexplored. This may be especially important for elucidating the factors and cognitive strategies that contribute to individual differences in context memory. Further work is already being undertaken in our lab to clarify the interaction between the effects of variation in attention at encoding and advanced age. We are currently recruiting and testing a sample of older adults on the AET to investigate this interaction.

Furthermore, while we believe that the current investigation utilizing fMRI with the AET allows for discerning functional brain activity underlying variations in attention at encoding as they relate to context memory, we believe that combining the task with electroencephalography (EEG) and eye tracking would provide additional insight on the temporal microstructure of the functional activation patterns involved. For example, time-locking the electric field potential changes using EEG with the encoding events and motor responses on the AET would provide clues about the time course of the neural activity underlying variations in attention at encoding with a resolution of the order of milliseconds. Additionally, saccadic eye movements may play a role in the coupling of attention and memory, at least during visual stimulus encoding (Hoffman et al., 2013; Staudigl et al., 2017), and may also provide novel insights into the time course and success of memory operations (Hannula, 2018). Accordingly, combining the AET with eye tracking may further our understanding of the task's temporal effects.

4.5 Conclusion and final remarks

"Outside of our laboratories we will all admit to—indeed, sometimes even marvel at—the striking differences in memory that exist among people" (Bors & MacLeod, 1996, p.411). This statement by Bors and MacLeod effectively captures the general motivation behind the work in this thesis. To summarize the contributions of the studies herein, the pattern of results suggest that (1) variation in attention during encoding impacts subsequent retrieval of context information and modulates posterior visual and motor-related brain regions (2) advanced age is associated with declines in context memory performance, but compensatory age-related upregulation of fronto-parietal and occipito-temporal regions at encoding supports subsequent associative context memory retrieval (3) Years of educational attainment and crystallized IQ do not account for individual differences in the aforementioned attentional effects or compensatory effects related to advanced age. While much work regarding individual differences in episodic memory remains to be done, we hope that findings from this body of research motivates researchers to move beyond crude measures of educational attainment and crystallized IQ, and alternatively examine factors that directly tap the neurocognitive processes of episodic memory task demands. Consequently, a more refined picture of factors that give rise to individual differences in memory, the underlying cognitive strategies, and functional activity patterns implicated may then be unraveled.

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