

NEURAL CORRELATES OF ITEM AND ITEM-CONTEXT MEMORY ENCODING

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The neural correlates of the formation of episodic memories – or memory for an item and its context – have been studied using a functional neuroimaging procedure known as the ‘subsequent memory procedure’. In this procedure, neural activity associated with later remembered versus later forgotten study items is contrasted and the identified brain regions – demonstrating ‘subsequent memory effects’ – can be considered candidate loci of neurocognitive operations supporting successful episodic encoding. The aim of the present work was to disambiguate the neural correlates of item and item-context (source) memory encoding, and investigate age-related differences in subsequent memory effects as well as the relationship between such effects and memory performance. The findings reported in Chapter

2 investigated whether age-related attenuation of negative subsequent item and item-item memory effects extends to the encoding of item-context memories. It is demonstrated that, unlike negative effects for item and item-item memory, encoding of negative effects for item-context associations does *not* attenuate with age and the level of disengagement of neural regions promotes better memory performance. The findings reported (from the same fMRI experiment as Chapter 2) in Chapter 3 addressed the question of whether the phenomenon of age-related over-recruitment of frontal regions during encoding extends to encoding of non-verbal materials. It is found that, contrary to prior studies utilizing verbal materials, recruitment of the right frontal cortex in task-stimuli combinations that promote bilateral effects in young subjects is *beneficial* for memory encoding. The experiment in Chapter 4 aimed to elucidate differences in the encoding of different context types. The results of this study suggest that negative effects differ depending on the type of source feature being encoded. The findings from these studies shed light on the circumstances under which older adults benefit from engagement/disengagement of different neural regions and the circumstances in which age-related changes in subsequent memory effects are observed.

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LIST OF ABBREVIATIONS

ANOVA – analysis of variance

AR – auto-regressive

BOLD – blood-oxygen-level-dependent

CVLT – California Verbal Learning Test

DMN – default mode network

DTI – diffusion tensor imaging

EPI – echo-planar image

ERP – event-related potential

FA – fractional anisotropy

FWHM – full width at half maximum

fMRI – functional magnetic resonance imaging

FOV – field of view

FSIQ – Full Scale Intelligence Quotient

GLM – general linear model

IFG – inferior frontal gyrus

IPS – intraparietal sulcus

LOC – lateral occipital cortex

MFG – middle frontal gyrus

MTL – medial temporal lobe

MNI – Montreal Neurological Institute

MP-RAGE – magnetization-prepared rapid gradient echo

MRI – magnetic resonance imaging

PFC – prefrontal cortex

ROI – region of interest

RT – reaction time

SD – standard deviation

SE – standard error

SPM – Statistical Parametric Mapping

TE – echo delay time

TR – repetition time

WAIS – Wechsler Adult Intelligence Scale

WTAR – Wechsler Test of Adult Reading

CHAPTER ONE

GENERAL INTRODUCTION

1.1 Introduction

One of the fundamental aspects of everyday living is the ability to encode and retrieve information about prior experiences. ‘Episodic memory’ refers to the neural and cognitive processes that support this ability – that is, the formation, storage, and retrieval of events that occur in a particular spatiotemporal context (Tulving 1983). Unlike other forms of memory such as memory for facts and knowledge (semantic memory) and memory for acquired skills (procedural memory), episodic memory is especially vulnerable to the effects of age (Nilsson 2003). Different explanations have been proposed for age-related decline in memory, including general ‘slowing’ or reduction in processing speed (Salthouse 1996), reduced attentional resources (Craik 1986), less inhibition of unwanted information (Hasher and Zacks 1988), and decrease in executive functioning (Buckner 2004). These different hypotheses for age-related memory decline are not independent, nor is each factor alone sufficient to account for decline in memory function (Light 1991; Luo and Craik 2008).

Memory performance in older individuals can be improved, however, with encoding tasks that encourage elaborative processing of items, as well as retrieval tasks that provide environmental support (see Craik and Rose 2012 for review). Older adults are less likely to deeply encode stimulus information, and thus benefit from the employment of encoding tasks that promote elaborative processing of stimulus items (Craik and Simon 1980). Additionally, older adults perform better at retrieval when administered a recognition memory test as opposed to a recall test requiring more effortful mental operations (Craik and McDowd

1987). One focus of the present body of work is comparing the neural activity associated with the formation of memories in young versus older individuals in circumstances where recognition memory performance is near-matched.

While the present body of work focuses on the *encoding* operations that support later recognition memory performance, it is important to note that encoding and retrieval cannot be studied in isolation. That is, in order to assess whether successful encoding has occurred, a retrieval memory test must be administered. Failure to retrieve information at test does not necessarily mean information was not encoded about the stimulus item at study. It could very well be that retrieval cues were insufficient to elicit memory for the desired study item or feature. Encoding and retrieval processes are also distinct from memory storage, which is difficult to experimentally investigate in humans and is not discussed in the present body of work.

1.2 Framework of Episodic Memory

Episodic memory is thought to be a consequence of operations performed ‘online’ at encoding (Rugg et al. 2002). By this ‘encoding specificity’ account, the way in which a stimulus item is processed at encoding determines the likelihood a retrieval cue will successfully elicit memory for that particular item (Tulving and Thomson 1973; Zeelenberg 2005). This has led to the notion of ‘transfer-appropriate processing’ (Morris et al. 1977), where greater overlap between processing engaged at encoding and retrieval is thought to promote better memory performance (Roediger et al. 1989; Nyberg et al. 2000). According to the theory of transfer-appropriate processing, there is not a specific ‘encoding circuit’ (Rugg

et al. 2008); rather, processes supporting encoding as assessed via the subsequent memory procedure (described below in Section 1.4) are task-specific (e.g. Otten and Rugg 2001; Otten et al. 2002; Fletcher et al. 2003; Mitchell et al. 2004; Park et al. 2008) and context specific (e.g. Uncapher et al. 2006; Uncapher and Rugg 2009; Gottlieb et al. 2010).

Processes engaged at encoding are thought to be captured by the medial temporal lobe, which integrates the information to form a comprehensive memory representation (Shimamura 2002; Shimamura 2010). At retrieval, the processes involved in the online processing of an item at encoding are thought to be ‘reactivated’ by a hippocampally-mediated mechanism, thus the memory representation is ‘cortically reinstated’ at retrieval (Norman and O’Reilly 2003). This theory of cortical reinstatement is, as pointed out by Rugg et al. (2008), complementary to the notion of transfer-appropriate processing and support for encoding-retrieval overlap has also been widely demonstrated (e.g. Wheeler and Buckner 2004; Woodruff et al. 2005; Wheeler et al. 2006; Johnson and Rugg 2007; Johnson et al. 2009).

Although the above theories of episodic memory intricately link together encoding and retrieval processes, the present work focuses on the different encoding processes that support later memory performance. Recognition memory performance is thought to be supported by two different processes. One of these processes, termed ‘recollection’, occurs when memory for an event is accompanied by details of the original experience of the event. A different process, termed ‘familiarity’, refers to when an event is recognized in the absence of any accompanying contextual features (Jacoby 1991; see Yonelinas 2002 for review).

‘Dual-process’ models of recognition memory view recollection and familiarity as distinct memory processes, where recollection is thresholded (all or none) and familiarity represents a continuous memory signal (see Diana et al. 2006 for review). In contrast, ‘single-process’ models uphold the view that recognition memory decisions are based on a single continuous memory strength index (Donaldson 1996). In this latter proposal, recollection and familiarity reflect ‘strong’ versus ‘weak’ memories and can be explained by high versus low confidence memory responses (Dunn 2004; see Wixted and Stretch 2004 for review). While there has been debate over whether dual-process versus single-process accounts are valid in conceptualizing recognition memory (Squire et al. 2007), the current body of work is guided by a dual process perspective.

Those that advocate a single-process signal detection model have demonstrated that ‘high confidence’ recognition (item) memory judgments are accompanied by a higher degree of contextual (source) information (Slotnick and Dodson 2005). Thus, measurements of source memory are often confounded by item memory strength (Squire et al. 2007). As such, the studies presented below incorporated an important methodological refinement where assessment of source memory was restricted to confident and correctly recognized study items.

1.3 Episodic Memory Tests

Different recognition memory paradigms have been developed to specifically index recollection. These include the ‘remember/know’ paradigm – where subjects are asked to respond ‘remember’ if memory for a test item is accompanied by contextual details and ‘know’ if they are confident the test item is old but are unable to recall any details (Tulving

1985; see Gardiner et al. 2002 for review) along with objective memory tests. Examples of objective memory tests include item-item and item-context (source) memory tasks (Mandler 1980; Jacoby and Dallas 1981). In item-item associative memory tests, pairs of items (e.g. word-pairs) are presented at study. At test, subjects are presented with study items that were previously paired together (intact), study items that were previous paired with other study items (rearranged), and new pairs. It is presumed that, because the single items of old and rearranged pairs are equally familiar, the ability to correctly identify intact from rearranged pairs is based on recollection (e.g. Yonelinas 1997; Donaldson and Rugg). Similarly, in source memory tests, subjects are presented with a series of items in typically one of two different encoding contexts (e.g. color background, font, study task). Subjects are asked to decide, at test, whether the item is old or new as well as which context was associated with the item at study. Recollection is operationalized as the ability to retrieve contextual (source) information associated with a test item.

While objective and subjective indices of recollection have been suggested to be functionally equivalent (Rugg et al. 1998), subjective measures of recollection (i.e. a remember/know memory test) have been shown to be more susceptible to age-related decline than objective measures such as a source memory test (Duarte et al. 2006). The present body work utilizes an objective measure to index recollection – specifically, an item-context (source) memory test. It is important to point out that although correct associative memory and source memory judgments are assumed to assess recollection, inability to recall the associated pair item or source feature does not mean accompanying features/details were not present. For example, when a subject is unable to remember which specific encoding context

was originally associative with a test item, this does not mean other ‘non-criterial’ features are not recollected about the item. ‘Non-criterial recollection’ (Yonelinas and Jacoby 1996) is thought to contribute, along with familiarity, to ‘associative miss’ or ‘source miss’ responses. Though non-criterial recollection was originally proposed to function as familiarity, it has been demonstrated that, along with age-related deficits in recollection compared to familiarity (Parkin and Walter 1992; Bastin and Van der Linden 2003; Howard et al. 2006), older adults also demonstrate impairments in non-criterial recollection compared to young adults (Toth and Parks 2006). Thus, it is important to emphasize that while successful associative memory judgments and retrieval of source memory features is held to index recollection, absence of criterial recollection is not equivalent to familiarity.

Moreover, it is important to note that different types of contexts have been utilized in source memory paradigms. One distinction that has been made is between ‘external’ sources, where information is present in the study environment, and ‘internal’ sources, where information is generated by the subject during study (Johnson et al. 1993; Taylor and Henson 2012). Examples of different types ‘external’ source contexts that have been commonly used include memory for color (Staresina and Davachi 2006; Staresina and Davachi 2008; Uncapher et al. 2006, 2009), location (Cansino et al. 2002; Park et al. 2008; Uncapher et al. 2006, 2009; Gottlieb et al. 2012), and sensory modality (Gottlieb et al. 2010, 2012; Park et al. 2012). A commonly used ‘internal’ source context is memory for the decisions made about an item at study (i.e. memory for encoding task; Davachi et al. 2003; Gold et al. 2006; Kensinger and Schacter 2006; Duarte et al. 2011).

Table 1.1 summarizes examples of source memory encoding studies in young adults. Though each of these source memory contexts is presumed to index recollection, little work has been done to directly compare different types of encoding contexts. A couple studies have instead combined encoding contexts, such as one of two colors signally one of two encoding tasks (Ranganath et a. 2004; Kirwan et al. 2008), making it difficult to determine whether effects are specific to one type of encoding context. Furthermore, a large proportion of these source memory studies in young subjects – including one encoding study by Staresina and Davachi (2008) which *does* compare 2 different types of contexts — have focused mainly on MTL regions (Davachi et al. 2003; Gold et al. 2006; Kirwan et al. 2008; Staresina and Davachi 2008; Duarte et al. 2011). An even larger proportion (all but three: Duarte et al. 2011; Gottlieb et al. 2010; Kirwan et al. 2008) have neglected to report whether negative subsequent memory effects (see below section) were present. It is not fully known whether different types of source memory contexts may elicit different patterns of effects outside the MTL.

1.4 Functional and Neural Bases of Episodic Memory Encoding

The advent of functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI) has allowed for the neural correlates of episodic memory to be investigated ‘in vivo’ in healthy human subjects. fMRI methods indirectly measure brain activity by taking advantage of the correlation between energy demands and cerebral blood flow. By application of a strong magnetic field, a blood-oxygen-level-dependent (BOLD) signal can be generated via differences in magnetic properties between oxygenated

hemoglobin and deoxygenated hemoglobin (Ogawa 1990). Though fMRI allows for good spatial resolution (on the order of millimeters), the temporal resolution is limited by the time course (multiple seconds) of the coupling between neural activity and vascular response, or ‘hemodynamic response’ (Logothetis 2002).

In fMRI studies of memory encoding, one procedure that has been widely employed is the ‘subsequent memory procedure’ (Paller and Wagner 2002). In this procedure, subjects are placed inside a scanner and presented with a series of stimuli. Outside the scanner, subjects are administered a recognition memory test and the neural activity corresponding to items that are later remembered is contrasted with the activity corresponding to items that are later forgotten. Regions that demonstrate differences in neural activity due to later memory – or a ‘subsequent memory effect’ – are posited to be involved in operations supporting the formation of an accessible memory representation.

Both ‘positive’ (later remembered > later forgotten) and ‘negative’ (later remembered < later forgotten) subsequent memory effects have been identified in the literature. Positive subsequent memory effects have consistently been identified in regions of left inferior frontal cortex, bilateral medial temporal lobe, fusiform cortex, bilateral premotor cortex, and bilateral posterior parietal cortex. In contrast, negative subsequent memory effects have commonly been identified in regions overlapping with the ‘default mode network’ (DMN), including inferior parietal, medial parietal, posterior cingulate, and superior frontal regions (see Kim 2011 for review). The contributions of medial temporal lobe, prefrontal cortex, and default mode network regions are outlined below, and are the main focus of this body of work.

1.4.1 *Medial Temporal Lobe (MTL)*

The MTL has been heavily implicated in studies of episodic memory. This focus has stemmed from studies of patients with MTL damage (especially the classic case of HM), where severe impairments in episodic memory have been found in patients with MTL lesions (Scoville and Milner 1957; Zola-Morgan et al. 1986; Squire 1992). Lesions that impair the hippocampus and surrounding MTL cortex appear to impact both recollection and familiarity, while hippocampal lesions result in selective deficits in recollection (Holdstock et al. 2002; Bastin et al. 2004; Mayes et al. 2004; Aggleton et al. 2005; but see Stark et al. 2002; Manns et al. 2003 for evidence of impaired recollection and familiarity in patients with hippocampal damage). As with all lesion studies, however, these patient studies do not allow for distinguishing between MTL contributions to encoding versus retrieval. Additionally, the paucity of patients with well-circumscribed lesions has made it difficult to study the specific contributions of different MTL subregions. Functional neuroimaging studies have enabled researchers to address both these issues, and this region has remained a spotlight in memory research.

Within the MTL, the hippocampus in particular is thought to be involved in the ‘binding’ of different stimulus features to form a comprehensive memory representation (Squire and Zola-Morgan 1991; Eichenbaum 1996; see Opitz et al. 2010 for review). This is supported by the findings of greater hippocampal activity at encoding for later remembered item-item (Sperling et al. 2001; Zeineh et al. 2003; Sperling et al. 2003; Kirwan and Stark 2004; Jackson and Schacter 2004; Prince et al. 2005; Sommer et al. 2005; Chua et al. 2007; Park and Rugg 2008; Qin et al. 2009; Westerberg et al. 2012; Park et al. 2012) as well as

item-context (e.g. Cansino et al. 2002; Ranganath et al. 2004; Staresina and Davachi 2006; Uncapher et al. 2006; Uncapher and Rugg 2009; Gottlieb et al. 2010; Duarte et al. 2011) associations.

Other subregions of the MTL, including the perirhinal cortex and parahippocampal cortex, are also thought play important roles in recognition memory (Squire et al. 2004; Strange et al. 2002; Davachi et al. 2006; Eichenbaum et al. 2007; Carr et al. 2010). Specifically, perirhinal cortex is thought to support familiarity-based recognition memory (Brown and Aggleton 2001; Diana et al. 2007; Eichenbaum et al. 2007; Mayes et al. 2007). fMRI studies demonstrating perirhinal cortex activation correlating with later item memory (but not source or associative memory) performance have supported this view (Davachi et al. 2003; Ranganath et al. 2004; Staresina and Davachi 2008). Some studies, however, have suggested that the perirhinal cortex supports memory for item-context associations (Staresina and Davachi 2006; Haskins et al. 2008). These studies suggest that the the perirhinal cortex is able to represent associations that have undergone ‘unitization’, where the paired items (or item and context) are treated as a single item (Staresina and Davachi 2010). The ability of the perirhinal cortex to support ‘familiarity-based’ associative recognition via unitization is consistent with patient data, where individuals with hippocampal/parahippocampal damage are found to be capable of forming memory for item-item associations if, for example, paired word items represent a compound word (Giovanello 2006; Quamme et al. 2007).

The parahippocampal cortex, like the hippocampus, has been thought to support recollection by the general processing of contextual features (Bar et al. 2008; Qin et al. 2007; Peters et al. 2009; Diana et al. 2012) and has demonstrated increased activity in studies of

item-item and item-context memory encoding (Davachi et al. 2003; Ranganath et al. 2004; Uncapher and Rugg 2005; Uncapher et al. 2006; Kensinger and Schacter 2006; Dougal et al. 2007). Different contributions of perirhinal cortex and parahippocampal cortex to recognition memory have also been attributed to their positions in the ventral visual ('what') and dorsal visual ('where') pathways, respectively. The perirhinal cortex is thought to be involved in processing object information while the parahippocampal cortex is thought to be involved in the processing of scene information (Litman et al. 2009; Diana et al. 2010; Ranganath 2010; Libby et al. 2012).

1.4.2 *Prefrontal Cortex (PFC)*

Another region that has been widely implicated in episodic memory encoding is the PFC. The PFC is thought to be important for organizing information during encoding, use of strategy, and monitoring and control of memory processes. Though patients with frontal lobe lesions have not demonstrated the same profound episodic memory deficits as those observed in patients with MTL damage, frontal patients have demonstrated subtle memory deficits, such as decline in recall (Dimitrov et al. 1999; Hildebrandt et al. 1998), elevated false alarm rates (Curran et al. 1997; Schacter 1996; Swick and Knight 1999), reduced semantic clustering (Gershberg and Shimamura 1995; Baldo et al. 2002), and impaired retrieval of contextual information (Janowsky et al. 1989; Shimamura et al. 1990; Smith and Milner 1988). However, in circumstances where demand for strategic control of retrieval processes is minimized, patients with damage to the PFC have demonstrated selective impairments in familiarity, but not recollection (Duarte et al. 2005; MacPherson et al. 2008; Aly et al. 2011)

Studies using fMRI have highlighted the role of the PFC in memory encoding. The left lateral PFC is thought to contribute to semantic processing, which is supported by the finding of increased activation in this region during verbal encoding tasks – for both intentional encoding tasks (Fletcher et al. 1995; Kapur et al. 1996; Kelley et al. 1998) as well as those in which encoding is incidental (Demb et al. 1995; Gabrieli et al. 1996; Wagner et al. 1998). Furthermore, subsequent memory effects in left PFC have been consistently demonstrated for verbal item memory (e.g. Wagner et al. 1998; Henson et al. 1999; Buckner et al. 2001; Otten et al. 2001; Baker et al. 2001; Reber et al. 2002; Chee et al. 2003; Uncapher and Rugg 2005) as well as verbal item-item associations (Habib and Nyberg 2008; Prince et al. 2007; Park and Rugg 2008; Haskins et al. 2008).

While much focus has been directed toward the encoding of verbal items, encoding of nonverbal items such as pictorial materials has been shown to produce increased activity in right lateral PFC (Brewer et al. 1998; Kelley et al 1998; McDermott et al. 1999; Floel et al. 2004; Hofer et al. 2007). Subsequent memory effects in right PFC have been reported for nonverbal item memory (Gutchess et al. 2005; Garoff et al. 2005; Sergerie et al. 2005; Dickerson et al. 2007) as well as nonverbal item-item associations (Qin et al. 2007). The finding of material-specific effects in left versus right PFC supports the notion that memory encoding is a byproduct of the processes engaged when an initial event is experienced.

Direct implications for the differential contributions of left and right PFC to verbal/non-verbal memory encoding have been demonstrated by inducing transient lesions via transcranial magnetic stimulation (TMS) in healthy subjects in both ventrolateral (Kohler et al. 2004; Gough et al. 2005; Hartwigsen et al. 2010; Machizawa et al. 2010) and

dorsolateral (Gagnon et al. 2009; see Balconi, 2013 for review). Consistent with fMRI effects, transient lesions of the left PFC have been found to disrupt encoding of verbal items while TMS of the right PFC has been found to disrupt encoding of nonverbal items (Floel et al. 2004; Gagnon et al. 2009). These studies demonstrate a causal role for the PFC in encoding and provide support for the notion that neural processes involved in the formation of episodic memories depend upon the content of the material being encoded.

Different PFC subregions – including dorsolateral, ventrolateral, and medial prefrontal regions – have been thought to differentially contribute to memory encoding (Fletcher et al. 1998; see Blumenfeld and Ranganath 2007 for review). The ventrolateral PFC, especially left inferior frontal gyrus (IFG), is thought to support memory encoding by mediating the selection and maintenance of goal-relevant item information and activating different semantic representations (Thompson-Schill et al. 1997; Thompson-Schill et al. 1999; Gold and Buckner 2002; Badre and Wagner 2007). In contrast, the dorsolateral PFC is thought to contribute to successful associative memory encoding by actively processing and organizing relational features during encoding (Blumenfeld et al. 2011). This is supported by the finding that activity in the dorsolateral PFC is predictive of associative memory but not item memory (Murray and Ranganath 2007; Qin et al. 2007; Addis and McAndrews 2006). Activity in the medial PFC is thought to reflect self-referential processing (Moran et al. 2006; Wang et al. 2012a; Kim and Johnson 2012) and predictive of later encoding of items for which judgments are made with regard to self (Macrae et al. 2004). This region is considered to be part of the default mode network, discussed below.

1.4.3 *Default Mode Network (DMN)*

Unlike PFC and MTL regions, the importance of DMN regions to episodic memory encoding did not arise as a result of patient data. The discovery of this network was unintended; early fMRI studies which sought to employ a passive ‘baseline’ from which to measure task-related neural activity consistently found a set of regions to be engaged during this ‘rest’ condition (Shulman et al. 1997; Buckner et al. 2012). This led to the theory of a ‘default mode’ of brain function, where regions were found to consistently demonstrate greater activity during resting states than during the engagement of goal-directed tasks (Binder et al. 1999; Mazoyer et al. 2001; Raichle et al. 2001; Greicius et al. 2003). The DMN consists of regions in the medial parietal cortex (particularly the precuneus), superior and inferior medial frontal regions, and posterior lateral parieto-occipital cortices (Gusnard and Raichle 2001). These regions are thought to reflect self-relevant processes and were initially described to be active during ‘random episodic silent thinking’ (i.e. ‘r.e.s.t.’; Andreasen et al. 1995). Further studies have since supported the notion that DMN regions are involved in spontaneous thought processes, processing of conceptual (‘internal’) sources of information, and in the formation of mental images (Binder et al. 1999; McKiernan et al. 2006; Addis et al. 2007). Activity in the DMN is therefore thought to reflect unconstrained and internally focused cognitive processes (for reviews see Buckner et al. 2008; Andrews-Hanna 2012).

The significance of this network to episodic memory is highlighted by the finding that regions demonstrating negative subsequent memory effects largely overlap with the DMN (Otten and Rugg 2001; Wagner and Davachi 2001; Daselaar et al. 2004; Daselaar et al. 2009). Though the functional significance of negative subsequent memory effects remains to

be fully elucidated, these effects are thought to reflect the benefit to encoding that occurs as a result of reallocating processing resources away from those supporting internal events to those supporting external events. It is important to emphasize, however, that the encoding of stimulus events is not universally supported by disengagement of DMN regions and the ‘deactivation’ of these regions is dependent on encoding task and stimulus content (Spreng et al. 2012). In particular, while the study of memory encoding has largely focused on external tasks (Callard et al. 2012), *increased* activity in DMN regions has been shown to support cognitive tasks that require self-processing and visuo-spatial imagery (Cavanna and Trimble 2006) as well as the encoding of self-referential and imaginative processes (Macrae et al. 2004; Hassabis et al. 2007; Kim and Johnson 2012). While it has been suggested that DMN regions may differentially support encoding depending on whether the event being encoded is an imagined (‘internal’) event versus an external event (Huijbers et al. 2011), a direct comparison of negative subsequent memory effects in the encoding of internal versus external encoding contexts has not been directly tested.

1.5 Effects of Age on Episodic Memory Encoding

Older individuals have widely shown to be impaired in their memory for the context in which a prior event occurred while maintaining memory for the event’s content compared to younger individuals (Spencer and Raz 1995). For example, early behavioral studies have demonstrated that older adults are less able to remember external source features such as color or location (Park et al. 1982; Park and Puglisi 1985), internal source features such as encoding context (Hashtroudi et al. 1989; Cohen and Faulkner 1989), or item-item

associations (Naveh-Benjamin 2000). These observations are in support of the notion that aging is associated with a selective impairment in recollection, with relatively little reduction in familiarity (Salthouse et al. 1997; Davidson and Glisky 2002).

Much of the work within the field of cognitive aging has focused on the neural and functional changes that may underlie age-related impairment in processes supporting recollection. Specifically, studies have employed functional neuroimaging methods to investigate whether the neural correlates of memory encoding differ as a function of age. These studies have largely been cross-sectional in nature, comparing neural effects in younger (20s) and older (60s-70s) individuals (Salthouse 2011). In cross-sectional fMRI studies of aging and memory, one confound to bear in mind is the possibility that differences in neural activity as a function of age are due to differences in memory performance. As such, much effort is made in the present body of work to ‘performance-match’ younger and older cohorts, with careful selection of older (and younger) subjects who are free from cognitive impairments and neurovascular risk factors. It is presumed that any differences in effects between younger and older subjects where these factors are tightly controlled for represent the lower bound of changes that occur in non-pathological cognitive aging (Rugg and Morcom 2004).

Table 1.2 summarizes studies that have employed the subsequent memory procedure to investigate age-related differences in the neural correlates of memory encoding and lists an overview of effects found in MTL, PFC, and DMN as well as their relationships with age. Patterns of age-related differences relevant to this body of work include the finding of increased bilaterality of frontal effects (Morcom et al. 2003; Duverne et al. 2009) as well as

decreased negative subsequent memory effects in DMN regions (Morcom et al. 2003; Gutchess et al. 2005; Miller et al. 2008; de Chastelaine et al. 2011; Mormino et al. 2012).

1.5.1 Aging and Medial Temporal Lobe (MTL)

Studies have reported volumetric loss in the MTL associated with normal aging (Raz et al. 2005; Bouchard et al. 2008; Fjell and Walhovd 2010; Rajah et al. 2010a), with hippocampal atrophy occurring at a greater rate than in other MTL subregions such as entorhinal cortex (Raz et al. 2004; Rodrigue and Raz 2004). Additionally, within the hippocampus, volumetric loss has been shown to demonstrate a posterior to anterior gradient with age, with greatest atrophy in posterior hippocampus (Ta et al. 2012). The significance of this age-related reduction in MTL volume to episodic memory is highlighted by the finding that MTL volume has been shown to be positively correlated with memory for everyday events in healthy older individuals (Bailey et al. 2013) and patients with mild cognitive impairment (Atienza et al. 2011). However, this notion of ‘bigger is better’ is by no means universally demonstrated, and differences in MTL volume do not seem to be sufficient in explaining age-related differences in episodic memory performance (Van Petten et al. 2004; Rajah et al. 2010a).

In studies of episodic memory encoding, encoding tasks have been found to elicit decreased hippocampal activation in older compared to younger subjects (Daselaar et al. 2003; Sperling et al. 2003; Trivedi et al. 2008), and some studies have found decreased subsequent memory effects in MTL regions (hippocampal and parahippocampal cortices) for item memory (Gutchess et al. 2005). Moreover, decreased hippocampal activation has been

associated with longitudinal decline in memory performance (Persson et al. 2011). Encoding studies that have more specifically indexed recollection, however, have demonstrated equivalent levels of hippocampal activation in younger and older subjects during the formation of item-item (associative) memories (Miller et al. 2008; de Chastelaine et al. 2011). However, it is unclear whether the hippocampus and subregions of the MTL are similarly activated in younger and older subjects during the encoding of item-context (source) memories. Age-related source memory deficits, for example, may be a consequence of age-related changes in the processing of stimulus content (see Awipi and Davachi 2008; Litman et al. 2009) and the regions involved in representing item and contextual information, as well as the binding of item-context representations may differ as a function of age.

1.5.2 *Aging and Prefrontal Cortex (PFC)*

One explanation that has been proposed for the selective age-related deficit in episodic memory is an age-related decline in frontal lobe functioning (Parkin and Walter 1992; Moscovitch and Winocur 1992; West 1996; Glisky et al. 2001). This ‘frontal lobe hypothesis’ of memory is bolstered by the finding that the PFC demonstrates accelerated atrophy with age compared to other brain regions (Raz and Rodrigue 2006; see Maillet and Rajah 2012 for review). It has therefore been suggested that many of the features of age-related changes in cognition – including episodic memory – can be attributed to age-related decline in the integrity of the PFC (West 1996; Glisky et al. 2001; Buckner 2004). While fMRI studies have focused on how age-related changes in PFC function impact memory (Grady 2008; Spreng et al. 2010) it is important to note that the PFC is not the only region to

demonstrate volumetric reductions with age, nor do changes in the functioning of the PFC fully explain age-related decline in episodic memory (see Spreng et al. 2010 for review).

Cross-sectional studies have reported different patterns of PFC activation in younger versus older adults. Some studies have demonstrated less PFC activity in older versus younger subjects (Brassen et al. 2009; Rajah et al. 2010b; Dulas and Duarte 2011), while others have reported increased PFC activity in older compared to younger subjects (Dennis and Cabeza 2008; Park and Reuter-Lorenz 2009). The latter such pattern – termed ‘age-related over-recruitment’ – is the finding that, relative to younger adults, older adults exhibit greater and more widespread encoding-related neural activity (Cabeza et al. 1997; Grady et al. 2005; Madden et al. 1999; Maguire and Frith 2003).

In studies of episodic memory encoding using verbal materials, older adults have been found to recruit prefrontal regions more bilaterally compared to the left-lateralized pattern observed in young adults (Logan et al. 2002; Rosen et al. 2002; Morcom et al. 2003; Duverne et al. 2009). Different theories have been proposed for this ‘age-related over-recruitment’, including the compensatory recruitment hypothesis (Cabeza 2002) and the dedifferentiation hypothesis (Li and Lindenberger 1999). The compensatory recruitment hypothesis proposes that older adults demonstrate greater and/or more widespread neural activity in order to compensate for age-related declines in performance (Cabeza 2002; Grady et al. 1995; Reuter-Lorenz et al. 2000; Park et al. 2001). The dedifferentiation hypothesis posits that over-recruitment is reflective of age-related pathological processes that result in less specialized neural recruitment (Li and Lindenberger 1999).

In older individuals, activity in the left prefrontal cortex associated with the encoding of verbal materials has been shown to be positively associated with memory performance (de Chastelaine et al. 2011). In contrast, engagement of right PFC for encoding of verbal items has been shown to be negatively associated with memory performance (Duverne et al. 2009; de Chastelaine et al. 2011). These findings suggest that, for verbal materials, the emergence of right frontal subsequent memory effects in older subjects does not index the engagement of compensatory processes that preserve memory performance in the face of age-related neural decline. An important question is whether the negative relationship between right frontal subsequent memory effects and memory performance observed for verbal materials depends upon the employment of study items and tasks that elicit strongly left-lateralized effects in young subjects.

1.5.3 Aging and Default Mode Network (DMN)

The importance of the DMN to cognitive aging has been highlighted by the finding that this network of regions is disrupted with normal age (Grady et al. 2006; Andrews-Hanna et al. 2007) and in individuals with Alzheimer's disease (Greicius et al. 2004). Healthy older adults have been found to demonstrate less activity in the default network at rest (Damoiseaux et al. 2008; Koch et al. 2010). Additionally, older subjects demonstrate reduced 'task-induced-deactivations' across different types of tasks (Grady et al. 2006, 2010), such as during the semantic processing of visually presented words (Lustig et al. 2003), verb generation (Persson et al. 2007), and encoding of spatial location (Gould et al. 2006). The decrease in deactivation of DMN regions observed in older adults has been

interpreted as a failure to efficiently reallocate resources and engage in task-related activity (Sambataro et al. 2010).

In studies of age-related differences in neural correlates of memory encoding, older adults have demonstrated attenuated negative subsequent memory effects compared to young adults. This age-related attenuation of negative effects has been demonstrated for item memory (Morcom et al. 2003; Duverne et al. 2009; Mormino et al. 2012) as well as item-item associations (de Chastelaine et al. 2011). In older individuals, the level of attenuation has been shown to be associated with poorer memory performance (Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2011; Mormino et al. 2012). In other words, the greater the magnitude of an older individual's negative effects in putative DMN regions, the better their performance on a later memory test. It is not known whether prior findings of the effects of age on negative subsequent associative memory effects extend to effects related to the encoding of item-context association, rather than item-item associations. Additionally, there is evidence to suggest that older subjects may demonstrate encoding tasks-specific reversals of negative subsequent memory effects, where self-referential encoding tasks give rise to different patterns of negative effects in older subjects compared to encoding tasks which do not reference self (Gutchess et al. 2010).

1.6 Summary

Functional neuroimaging studies over the past decade have attempted to address the cognitive operations and neural correlates of episodic memory encoding and how these neural correlates change in the context of normal aging. The subsequent memory procedure

has been used to identify specific regions in episodic memory processing that demonstrate differential activity according to later memory. Studies in young adults have consistently identified positive subsequent memory effects in regions of PFC, hippocampus, and adjacent MTL cortex, as well as negative effects in medial parietal regions associated with the default mode network. There is still much work to be done on how these effects change with age, as well as the functional significance of these effects. For instance, while it is known that older subjects demonstrate bilateral frontal (as opposed to left-lateralized) effects for verbal materials, it is not known whether recruitment of the right hemisphere in older subjects supports encoding of non-verbal materials. This question is addressed in Chapter 2.

Furthermore, while several studies have demonstrated attenuated negative effects in older subjects for item and item-item memory encoding, it is not known whether this finding extends to the encoding of item-context associations. This question is addressed in Chapter 3. Chapter 4 investigates the differences in encoding-related activity associated with the encoding of ‘internal’ versus ‘external’ contexts. Together, these findings provide evidence that, the phenomenon of ‘right frontal over-recruitment’ in older subject does not apply to the encoding of pictorial materials in circumstances where item memory strength is matched in younger and older subjects. Additionally, these findings provide evidence that the inability of older subjects to differentially modulate default mode network regions for item and item-item associative memory encoding does not apply to the encoding of item-context associations. This may, however – as the findings in Chapter 4 suggest – depend on the type of context being encoded. The general significance of these findings is discussed in Chapter 5.

Table 1.1 (pg 1 of 2) Subsequent memory studies of source memory encoding in young subjects

Author	Item	Context	Encoding Task	Retrieval Task	Conditions	MTL Effects	Frontal Effects	Negative Effects
Cansino et al. 2002	Pictures	One of 4 spatial locations	Artificial/Natural judgment	Upper L, Upper R, Lower L, Lower R, New	Source H, Source M	Source: none found	Source: L SFG, L IFG, B PCG	Not reported
Davachi et al. 2003	Words (adjectives)	One of 2 encoding tasks (mental image, read)	Imagine scene (critical items) or read backward; indicate success (1-4)	(20h later) Old/New; Image/Read	Source H, Source M, Item M	Item: L PrC; Source: B Hc, L PHc	Not reported	Not reported
Duarte et al. 2011	Words, Objects, Scenes	One of 2 encoding tasks (pleasantness, commonness)	Pleasantness or Commonness judgment	Pleasant/Common/New; Confidence (1-3)	High Conf Source H, (Med+Low Conf Source H)	Source (words, objects, scenes): B Hc, L PHc	Source (all items): L MFG, L PrG; Source (words): L IFG	Source (all items): B MCC, R IFG, R MFG; Source (objects): L PrC, B MCC, R PCC, B PCG
Gold et al. 2006	Words (adjectives)	One of 2 encoding tasks (visualize indoor vs outdoor)	Visualize 'indoor' vs 'outdoor' scene corresponding to word	1-6 Scale Old-New; 1-6 Scale Indoor vs Outdoor	Item H, Source H, Source M	Item: L Hc, R PrC	None reported	Not reported
Gottlieb et al. 2010	Pictures	One of 2 modalities	Does auditory/visual label correspond	Old/New; Visual/Auditory/Don't Know Source	Visual H, Auditory H, Visual M, Auditory M	Source (aud, vis): L ant MTL	Source Memory (aud, vis): B IFG	Not reported
Gottlieb et al. 2012	Pictures	One of 2 locations; One of 2 voices (male/female)	Picture and spoken name congruent	Old/New; Left/Right/Unsure; Male/Female/Unsure	Both Source H, Location H, Voice H, Source M	Source (loc, voice): R Hc; Source (location): L Hc, L PHc	None reported	Source (loc, voice): B MPC, B OFC; Source (voice): R SFG
Kensinger and Schacter 2006	Words and Pictures (positive, negative, neutral)	One of 2 encoding tasks	Animacy or Commonness judgement	Old-Animacy, Old-Commonness, New	Word Source H, Picture Source H, Word Source M, Picture Source M, Item M	Item (pic,word): L PHc; Source (word,pic): L Hc; Source (pic): R Hc, R PHc	Item (pic, word): L SFG, L IFG; Source (pic,word): L SFG; Source (pic): L MFG	Not reported
Kirwan et al. 2008	Words	One of 2 font colors cuing one of 2 encoding tasks (size vs animacy)	Size or Animacy judgment	1-6 Scale Old-New; 1-6 Scale Size vs Animacy	Item Strength 1-6; Source Strength 1-6	Item Strength (linear increase): B Hc, R PrC; Source: no MTL regions when item strength held constant	Item Strength: L MFG; Source: L mPFC, R vIPFC	Item Strength: B LPC, R PPC, R insula

Abbreviations: H=hit; M=miss; L=left; R=right; B=bilateral; Hc=Hippocampus; PrC=perirhinal cortex; PHc=Parahippocampus; MTL=medial temporal lobe; IFG=inferior frontal gyrus; MFG=middle frontal gyrus; SFG=superior frontal gyrus; mPFC=medial prefrontal cortex; dlPFC=dorsolateral PFC; vlPFC=ventrolateral PFC PrG=precentral gyrus; MCC=middle cingulate cortex; PCC=posterior cingulate cortex; MPC=medial parietal cortex; LPC=lateral parietal cortex; PPC=posterior parietal cortex; OFC=orbitofrontal cortex

Table 1.1 (pg 2 of 2) Subsequent memory studies of source memory encoding in young subjects

Author	Item	Context	Encoding Task	Retrieval Task	Conditions	MTL Effects	Frontal Effects	Negative Effects
Park et al. 2008	Words	One of 2 different locations in one of two different frame colors	Syllabic task for 1/2 of study, animacy task for other 1/2 of study	Old/New; Left, Right, Unsure	Source H, Source M, Item M	Item (syllable): L ant MTL; Source (animacy): R Hc (reduced threshold)	Item: R mPFC (both tasks), L dlPFC (animacy task), L vlPFC (syllable task)	Not reported
Ranganath et al. 2004	Words	One of 2 font colors cuing one of 2 encoding tasks (animacy vs size)	Animacy or Size judgment	1-6 Scale Old-New; Red vs. Green	Source H, Source M, Item M	Item Strength (linear increase): L PHc; Source: R Hc, R PHc	Item Strength (linear increase): L IFG, L SFG, L PrG; Source: B IFG, B precentral gyrus	Not reported
Staresina and Davachi 2006	Words (nouns)	One of four background colors (red, yellow, green, blue)	Create mental image of word in color indicated by background, indicate plausible vs. unplausible	Free Recall + 2-step recognition (Old/New; red,yellow,green,blue)	Free Recall, Source H, Source M, Item M	Source Memory: L perirhinal cortex	Source: L IFG; Free Recall > (Source Hit, Source Miss); L dlPFC	Not reported
Staresina and Davachi 2008	Words (nouns)	One of four background colors + one of 2 encoding tasks	Plausibility or Pleasantness judgment of item in color indicated	Old/New; Color judgment/DK; Plausibility/Pleasantness/DK	Color+Task H, Task H, Color H, Source M, Item M	Source (color, task): L Hc; Source (color): B PrC	None reported	Not reported
Uncapher et al. 2006	Words	One of four colors + one of four locations	Animacy judgment (for critical study items)	Old/New; Color judgment; Location judgment	Loc+Color H, Loc H, Color H, Source M, Item Miss	Item: L PrC; Source: R Hc (reduced threshold)	Item: L IFG; Source (loc, color): L IFG, L PrG	Not reported
Uncapher and Rugg 2009	Pictures	One of four colors + one of four locations	Size judgment (for critical study items)	Old/New; Color (1-4); Location (1-4)	Loc+Color H, Location H, Color H, Source M, Item Miss	Source: B Hc, L PHc	Item: B IFG, L PrG; Source: L PrG	Not reported

Abbreviations: H=hit; M=miss; L=left; R=right; B=bilateral; Hc=Hippocampus; PrC=perirhinal cortex; PHc=Parahippocampus; MTL=medial temporal lobe; IFG=inferior frontal gyrus; MFG=middle frontal gyrus; SFG=superior frontal gyrus; mPFC=medial prefrontal cortex; dlPFC=dorsolateral PFC; vlPFC=ventrolateral PFC PrG=precentral gyrus; MCC=middle cingulate cortex; PCC=posterior cingulate cortex; MPC=medial parietal cortex; LPC=lateral parietal cortex; PPC=posterior parietal cortex; OFC=orbitofrontal cortex

Table 1.2 Subsequent memory studies of aging and memory encoding

Study	Stimuli	Encoding Task	Retrieval Task	Conditions	MTL Effects	PFC Effects	Negative Effects
Dennis et al. 2008	Face-scene pairs	N-back (n=2)	Old/New (Conf 1-4)	High conf H, (Low conf H + M)	Y>O: B PHc (scene), B Hc (face-scene)	Y>O: Face: B dlPFC (face-scene), B SFG (face-scene), L dlPFC (face), L vlPFC (face); O>Y: B dlPFC (scene)	Not reported
de Chastelaine et al. 2011	Word pairs	Which fits in which?	Intact, Rearranged, New	Associative H, Associative M	Y=O: R Hc	Y=O: L SFG, L IFG	Y>O: B MFG, R SFG, R PCC, R MTG, R IPC
Duverne et al. 2009	Words	Animacy judgment	Old/New (Conf 1-4)	High conf H, (Low conf H + M)	Y=O: L Hc	O>Y: R PFC; Y=O: L IFG, L SFG	Y>O: PCC; Y=O: B MPC, R LPC;
Gutchess et al. 2005	Scenes	Does scene contain water?	High/Low Conf Old, New	High Conf H, Item M	Y>O: B PHc	Y=O: B vlPFC	Y>O: B mPFC, B ACC
Gutchess et al. 2010	Words (adjectives)	One of three orienting conditions (self/other/case)	Old/New	Item H, Item M	Not reported	Not reported	Y>O: B ACC, L mPFC, R PCC, L vlPFC
Kukolja et al. 2007	Pictures (one of four spatial locations)	Natural vs. Artificial judgment	Old/New; Location (1-4)	Source Correct, Source Incorrect	Y=O: R Hc (reduced threshold)	Not reported	Y=O: R ant insula, R MFG
Miller et al. 2008	Face-name pairs	Is name good fit for face?	Forced choice, High/Low Conf	High Conf H, M	Y=O: B Hc	Y=O: B IFG	Y>O: L MFG, L MTG, L IPC, L Pcu
Morcom et al. 2003	Words	Animacy judgment	Old/New (Conf 1-4)	High conf H, (Low Conf H + M)	Y>O: L Hc; R PHc	O>Y: R PFC; Y=O: LIFG, L dlPFC	Y>O: B antPFC
Mormino et al. 2012	Scenes	Does scene contain water?	Old/New (Conf 1-4)	High Conf Item H, Item M	Y=O: R PHc, R Hc	Y=O: B IFG	Y>O: B PCu, R mPFC, B SMG

Abbreviations: Conf=confidence; L=left, R=right, B=bilateral, H=hit, M=miss, Y=young, O=old, Hc=hippocampus, PHc=parahippocampus, SFG=superior frontal gyrus; IFG=inferior frontal gyrus; antPFC=anterior PFC; dlPFC=dorsolateral PFC; vlPFC=ventrolateral PFC; mPFC=medial PFC; PCu=Precuneus; ACC=anterior cingulate cortex; SMG=supramarginal gyrus; PCC=posterior cingulate cortex; IPC=inferior parietal cortex; MTG=middle temporal gyrus

CHAPTER TWO
EFFECTS OF AGE ON NEGATIVE SUBSEQUENT MEMORY EFFECTS
ASSOCIATED WITH THE ENCODING OF ITEM AND ITEM-CONTEXT
INFORMATION

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2.1 Introduction

Episodic memory – memory for unique events – declines markedly and, compared to other kinds of memory, disproportionately with increasing age (Nilsson 2003). A considerable body of work, much of it involving functional neuroimaging, has focused on elucidating the cognitive and neural bases of episodic memory decline. Many of these studies have focused on whether there are age-related differences in the neural correlates of episodic memory encoding, employing the fMRI ‘subsequent memory procedure’ (Paller and Wagner 2002) in an effort to identify such differences. In this procedure, encoding-related activity associated with study trials that are later remembered is contrasted with the activity elicited on trials that are later forgotten (identifying so called ‘subsequent memory effects’). Two classes of subsequent memory effect can be identified (see Kim 2011 for review). One class – the most heavily investigated both in studies confined to young subjects and in aging studies – takes the form of enhanced study activity for later remembered relative to later forgotten trials. The other class, known as ‘negative’ subsequent memory effects, takes the reverse form – namely, a relative diminution of study

activity for trials that go on to be remembered. It is this second class of effects that is the focus of the present paper.

As documented in the meta-analysis of Kim (2011; see also Otten and Rugg 2001; Wagner and Davachi 2001; Clark and Wagner 2003; Daselaar et al. 2004; Reynolds et al. 2004; Park and Rugg 2008, for examples), negative subsequent memory effects in young individuals have consistently been reported in a characteristic set of brain regions, including medial parietal and posterior cingulate cortex, medial prefrontal cortex, and lateral parietal cortex. As noted by several authors (e.g. Daselaar et al. 2004; Kim 2011; Park and Rugg 2008; Shrager et al. 2008; Turk-Browne et al. 2006), these regions form part of the ‘default mode network’, a set of brain regions that collectively exhibit task-related deactivation (greater activity during ‘rest’ than during task engagement) and whose resting state activity is inter-correlated (e.g. Raichle et al. 2001; Buckner et al. 2008). This network is of relevance to cognitive aging because task-induced deactivations in default mode regions are significantly reduced in healthy older subjects compared to young subjects (e.g. Lustig et al. 2003; Grady et al. 2006; Persson et al. 2007; Sambataro et al. 2010) and are further reduced in patients with mild cognitive impairment (Rombouts et al. 2005) and Alzheimer’s disease (Greicius et al. 2004; Lustig et al. 2003). Default mode network regions are believed to support ‘internally-directed’ processes that must be disengaged in order to permit optimal allocation of processing resources to an external event (such as a study item). Although the functional significance of negative subsequent memory effects remains to be fully elucidated, negative effects in putative default regions are thought to reflect the benefit to

encoding that results from redirecting processing resources from internally directed cognition to an external event (Daselaar et al. 2004; Huijbers et al. 2013).

Importantly, age-related differences in default mode activity are accompanied by analogous differences in negative subsequent memory effects. Several studies have reported that the effects are attenuated, or even reversed, in older subjects during the encoding of single items (Morcom et al. 2003, Gutchess et al. 2005; Duverne et al. 2009; Mormino et al. 2012) or item-item associations (Miller et al. 2008; de Chastelaine et al. 2011). In four of these studies (Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2011; Mormino et al. 2012) the magnitude of negative effects in older individuals was positively correlated with their memory performance, suggesting that the effects reflect the engagement of processes beneficial to memory encoding.

The primary motivation for the current study derives from prior reports of age-related attenuation in negative subsequent memory effects for the encoding of inter-item associations (face-name pairs in Miller et al. 2008; word pairs in de Chastelaine et al. 2011). Unlike recognition memory for single items, which can be supported both by retrieval of episodic information and a separate, acontextual sense of familiarity (Yonelinas 2002), memory for item-item associations is held to depend heavily upon episodic retrieval ('recollection'). Thus, the findings from these studies suggest that the failure to appropriately modulate default mode activity during encoding plays an important role in age-related episodic memory impairment.

The present study builds on these prior findings by addressing the question of whether the age-related attenuation of negative subsequent memory effects reported for the encoding of item-item associations extends to the encoding of item-*context* associations (source memory). Like inter-item associations, memory for item-context associations is also held to depend heavily on recollection of episodic information, with little contribution from familiarity (Mickes et al. 2010). Moreover, again like memory for inter-item associations (e.g. Naveh-Benjamin 2000), source memory is markedly affected by age (e.g. Spencer and Raz 1995; Glisky et al. 2001; but see Siedlecki et al. 2005). Thus, if the failure to disengage default mode activity plays a role in age-related episodic memory decline, as was proposed above, older subjects should demonstrate the same pattern of attenuated negative subsequent memory effects for the encoding of item-context associations as they do for the encoding of item-item associations.

Importantly, the present study incorporated a methodological refinement motivated by the fact that the distinction between successful and unsuccessful source memory tends to be confounded with the strength of item memory (accuracy and confidence of item recognition are higher for items that go on to elicit accurate rather than inaccurate source judgments; Squire et al. 2007; Kirwan et al. 2008; Wais et al. 2010). To control for the confounding effects of memory strength, subjects made confidence judgments for both item and source judgments. Items receiving a ‘confident old’ judgment were segregated according to whether they went on to be given an accurate, highly confident source judgment (‘source hit’) or an inaccurate/uncertain context judgment (‘source miss’). Studied items that were recognized with low confidence or misclassified as new were assigned to a separate

category. Thus, the contrast between source miss and source hit trials permitted identification of the neural correlates of strong item-context associations unconfounded by differences in item memory strength. Correspondingly, the contrast between ‘item miss’ and source miss trials permitted the identification of the neural correlates of the encoding of memories supporting high confidence item judgments in the absence of associated source information.

2.2 Materials and Methods

2.2.1 Subjects and neuropsychological testing

Seventeen healthy young adults (11 females) aged between 18 and 27 years (mean age: 20 yrs), and 25 healthy older adults (16 females) aged between 63 and 74 years (mean age: 67 yrs) participated in the experiment. Young adults were recruited from the undergraduate and graduate student population of University of California, Irvine (UCI), and older adults were recruited from the Orange County community. All subjects were screened for histories of neurological, cardiovascular, or psychiatric illness, and contraindications for MR imaging. While none of the subjects were taking CNS-active medication, two older subjects were taking antihypertensive medication. All subjects had normal or corrected-to-normal vision, were right-handed, and learned English as their first language. Subjects gave informed consent prior to participating, and were remunerated for their participation in accordance with the human subjects procedures approved by the Institutional Review Board at UCI.

Potential subjects were excluded if they scored 1.5 standard deviations below their age-appropriate norm on the California Verbal Learning Test-II (CVLT), below 100 on the Full Scale Intelligence Quotient (FSIQ) (estimated from the Wechsler Test of Adult Reading (WTAR)), or more than 1.5 standard deviations below the age-appropriate norm on any two of the other neuropsychological tests described below. Data collected from one younger adult and two additional older adults were excluded from all analyses because of excessive head movement (>3 degrees of rotation) during scanning. Data from one other older adult were excluded because of abnormal signal in sub-insular regions in the structural scans.

In a separate session prior to the fMRI procedure, a battery of standardized neuropsychological tests was administered to all subjects. The battery assessed a range of cognitive functions known to either decline or to be maintained with age. The Mini Mental State Examination was utilized as a dementia screening measure, where a cut-off score of 26/30 was adopted. Long-term memory was assessed with the California Verbal Learning Test-II and the Wechsler Memory Scale-IV Logical Memory II. Short-term memory was assessed with the Digit Span Forward and Backward test of the Wechsler Adult Intelligence Scale-Revised (WAIS-R). General cognitive functions were further assessed with the Digit/Symbol Coding test of the WAIS-R, the Trail Making Test A and B, and letter fluency and category fluency tests.

An estimate of full-scale IQ was obtained from the Wechsler Test of Adult Reading. The Geriatric Depression Scale was also administered to older subjects.

2.2.2 Stimulus materials

Three hundred thirty-two stimulus pictures were used in the experiment. The colored pictures depicting everyday objects were drawn from Hemera Photo Objects 50,000 Volume III. Of the 332 pictures, 12 served as buffers (two at the beginning and end of each study list and test list) and 50 additional pictures were used as practice items before the study and test phases. Of the remaining 270 pictures, 180 were assigned to the ‘study’ condition while 90 were assigned as ‘new’ items.

Two study lists were created from the 180 study pictures for each subject. Each picture list contained a pseudo-randomized ordering of 90 pictures (45 ‘size’ and 45 ‘where’ judgments) and 30 null trials, with no more than three consecutive presentations of items belonging to the same encoding task. Test items comprised the 180 pictures from the study trials and 90 new pictures and were pseudo-randomized such that there were no more than three consecutive presentations of items belonging to the same experimental condition. All experimental stimulus display was implemented using the Cogent software package (<http://www.vislab.ucl.ac.uk/cogent.php>).

2.2.3 Experimental tasks and procedures

The experimental procedure consisted of a study task which took place during scanning, followed by a recognition memory test on a computer outside the scanner 20-25 minutes after the end of the scanning session. Prior to the scanning session, each subject was

administered a 2 minute practice study (24 pictures, 7 ‘null’ events). Both a seven-minute structural scan and twelve-minute diffusion tensor imaging (DTI) scan were conducted prior to the study phase. Immediately prior to the study phase a second 1-minute practice session was administered inside the scanner.

Study Phase

Two blocks of pictures (stimuli described above) were administered, separated by a 1-minute break. The requirement was to make a size or location judgment depending on a one-letter study cue preceding the stimulus picture: ‘S?’ for a size judgment (bigger or smaller than a shoebox) and ‘W?’ for a where judgment (indoors or outdoors). Instructions emphasized the need to respond quickly, but without sacrificing accuracy. Subjects were told their memories for the pictures would be tested later, but they were not informed of the source memory test (‘size’ vs. ‘where’).

During each study trial the study cue was displayed for 500 ms (Helvetica, 30 point font) followed immediately by a study picture which was presented for 1500 ms. The study picture was replaced with a white fixation cross in the same font and size as the study cue for 2150 ms, which was switched to a red fixation cross for 500 ms signaling the end of the trial. The stimulus onset asynchrony of study trials was distributed stochastically with a minimum duration of 4150 ms modulated by the additional 60 null trials (Josephs and Henson, 1999).

Study items were back-projected onto a screen and viewed via a mirror mounted on the scanner head coil. Pictures were presented in central vision and subtended a maximum visual

angle of $9.5^\circ \times 9.5^\circ$ in horizontal and vertical directions. Study task responses were made with the right index and middle fingers via a hand-held button. The assignment of each finger to the smaller/indoors or larger/outdoors response was counterbalanced across subjects.

Test Phase

After completion of the study session, subjects were removed from the scanner. They were then informed of the source memory test and given instructions and a short (34 item) practice test. The test requirement was to judge whether the item had been presented at study and, if so, to indicate which encoding task had been associated with the picture at study.

The test pictures were presented in central vision, and subtended $5.7^\circ \times 5.7^\circ$ visual angles at the 1 m viewing distance. Instructions were to make an old/new judgment on a 5-point confident scale, the options for which appeared below the picture in white letters: ‘Conf-Old’, ‘Unconf-Old’, ‘Do-not-know’, ‘Unconf-New’, ‘Conf-New’. If one of the categories ‘Do-not-know’/‘Unconf-New’/‘Conf-New’ was selected, the test advanced to the next item. If a ‘Conf-Old’ or ‘Unconf-Old’ response was made, an encoding context judgment was required: ‘Conf-S’, ‘Unconf-S’, ‘Do-not-know’, ‘Unconf-W’, or ‘Conf-W’.

The hands employed for old and don’t know/new responses were counterbalanced across subjects, with middle/index finger of one hand assigned to ‘Conf-Old’/‘Unconf-Old’ respectively and index/middle/ring finger of the other hand assigned to ‘Do-not-know’/‘Unconf New’/‘Conf-New’ respectively. Size/where responses were also counterbalanced with ‘Conf-S’/‘Unconf-S’ and ‘Do-not-know’/‘Unconf-W’/‘Conf-W’

judgments assigned to separate hands. The test was self-paced, presented as a single block, and lasted approximately 25 minutes.

2.2.4 MRI Data Acquisition

A Philips Achieva 3T MR scanner (Philips Medical Systems) equipped with a transmit/receive radio frequency head coil was used to acquire anatomical and functional images. Functional scans were acquired with a T_2^* -weighted echo-planar image (EPI) sequence using the following parameters: TR 2 s, TE 30 ms, flip angle 70° , FOV 240x240, matrix size 80x79. Each EPI volume was acquired in ascending order and consisted of 30 slices, (3 mm thick with 1 mm interslice gap), oriented parallel to the line connecting anterior and posterior commissures, and positioned for full coverage of the cerebrum and most of the cerebellum. Functional data were acquired during each of the two study blocks (266 volumes per block) and concatenated across sessions prior to model estimation. The first three volumes were discarded to allow tissue magnetization to achieve a steady state.

T_1 -weighted anatomical images were acquired using a 3D magnetization-prepared rapid gradient echo (MP-RAGE) pulse sequence with the following parameters: FOV=240x240, matrix size 220x193, voxel size 1x1x1mm, 150 slices, sagittal acquisition. Although not reported here, diffusion tensor images were also acquired for each subject.

2.2.5 MRI Data Analysis

Data were preprocessed and analyzed with Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK; Friston et al. 1995) implemented under Matlab2008b (Mathworks Inc., USA). Volumes were motion and slice-time corrected, realigned and then spatially normalized using a sample-specific template. The sample-specific template was created by first normalizing (Ashburner and Friston 1999) the initial volume of each subject's functional time series with reference to a standard EPI template based on the MNI reference brain (Cocosco et al. 1997). Normalized volumes were separately averaged within each age group and the resulting two mean images were then averaged to generate a sample-specific template that was equally weighted with respect to each age group. Normalized volumes were resampled into 3 mm isotropic voxels, and smoothed with an isotropic 10 mm full-width-half-maximum (FWHM) Gaussian kernel to accommodate residual anatomical variation between subjects. T_1 -weighted anatomical images were normalized with a procedure analogous to the functional images and resampled into 2 mm isotropic voxels.

Stimulus-elicited neural activity was modeled for each subject by convolving a delta function with two hemodynamic response functions (HRFs). The two functions consisted of a canonical ('early') HRF as implemented in SPM (Friston et al. 1998) and delayed ('late') HRF that was generated by temporally shifting the canonical HRF by one TR (2 s), and was included to capture possible delayed responses. The late function was orthogonalized with respect to the early function using the Gram-Schmidt procedure so as to give priority to the

canonical function (Andrade et al. 1999). The findings for the late function did not add substantially to those obtained with the early function, and are not reported here.

The design matrix of the GLM included five early and five late covariates that modeled events defined by subjects' responses during the test phase. Three events of interest were identified for the fMRI analyses: (1) studied items correctly and confidently endorsed as old that were associated with confident correct context response ('source hit'); (2) items correctly and confidently endorsed as old followed by an incorrect or 'don't know' context response ('source miss'); and (3) items that were either unrecognized or judged old with low confidence ('item miss'). A fourth category consisted of items correctly and confidently judged old followed by a correct source judgment of low confidence. These trials were modeled separately and not included in the fMRI analysis. The fifth category of trials comprised events of no interest, namely buffer trials and trials associated with omitted or multiple study responses. Six regressors modeling concatenated movement-related variance (three rigid-body translations and three rotations determined from the realignment stage) and session-specific constant terms modeling the mean over scans in each session were also entered into the design matrix.

The functional time-series for each voxel was highpass-filtered to 1/128 Hz and scaled within-session to a grand mean of 100 across voxels and scans. Nonsphericity of the error covariance was accommodated by an AR(1) model, in which the temporal autocorrelation was estimated by pooling over suprathreshold voxels (Friston et al. 2002). The parameters for each covariate and the hyperparameters governing the error covariance were estimated

using a Restricted Maximum Likelihood (ReML) approach. Parameter estimates derived from each covariate were taken forward to the second level of analysis.

To identify voxels that differentiated the three events of interest in an unbiased manner, the respective parameter estimates were subjected to a 2 x 3 mixed-design ANOVA with factors of age group (young, older subjects) and response category (source hit, source miss, item miss) using the statistical methods implemented in SPM8. Pairwise contrasts (t-maps) derived from the ANOVA model were thresholded at $p < .001$, 1-tailed. Interaction contrasts (F maps) were thresholded at $p < .001$, 2-tailed. Control of Type I error was effected by imposing a cluster-wise threshold of $p < .05$, corrected for multiple comparisons within a whole-brain mask. The threshold was set at 24 contiguous voxels on the basis of a Monte Carlo simulation implemented in the Alphasim routine of the AFNI analysis package (NIMH, Bethesda; <http://afni.nimh.nih.gov/afni>)

2.3 Results

2.3.1 Neuropsychological Data

Demographic and neuropsychological data for older and younger subjects are summarized in Table 2.1. As can be seen from the table, the groups were well-matched on estimated IQ (Wechsler Test of Adult Reading) and performed comparably on tests of digit span and letter/category fluency. Older adults demonstrated significantly lower performance on some tests of long term memory (CVLT composite recall and false positive scores), but

not others (Wechsler Memory Scale-IV Logical Memory II), and demonstrated significantly lower performance on tests requiring speeded cognition (Trail Making A and B; Digit/Symbol Substitution).

2.3.2 Behavioral Results

Study Phase

Reaction times (RTs) to study items are given in Table 2.2 segregated according to subsequent memory condition. To assess whether RT varied with age group or later memory, ANOVA with factors of memory condition for the fMRI analysis (source hit, source miss, item miss) and age group (young, older subjects) was performed. There was no main effect of group ($F_{(1,40)} < 1$), nor was there a significant interaction between group and subsequent memory condition ($F_{(1,9,74.0)} < 1$). There was, however, a main effect of subsequent memory condition ($F_{(1,9,74.0)} = 13.26$, $p < .001$). Follow up analyses revealed that the effect reflected significantly shorter study RTs for source hit trials than source miss trials ($F_{(1,40)} = 7.70$, $p < .01$) and significant longer RTs for source miss relative to item miss trials ($F_{(1,40)} = 27.62$, $p < .001$). Additionally, RTs for source hit trials were significantly longer than those for item miss trials ($F_{(1,40)} = 5.03$, $p < .05$). RTs thus followed the pattern of item miss < source hit < source miss.

Test Phase

Item Memory: Table 2.3 shows performance on the later memory test. Mean item hit rates (correct ‘old’ judgments to old items, collapsed across confidence and source accuracy) were

.83 (SD=.06) for young and .76 (SD=.11) for older subjects. Mean item false alarm rates (incorrect 'old' judgments to new items, collapsed across confidence and source accuracy) were .03 (SD=.03) and .04 (SD=.05) for young and older subjects, respectively. Item memory performance (pHit-pFalse Alarms) was significantly lower for the older group compared to the younger group ($t_{40}=2.97$, $p=.005$), with values of .81 (SD=.08) and .72 (SD=.13) for the young and older subjects, respectively. When subjects made a 'confident old' response to an item, however, there was no difference in the accuracy of the judgments (as measured by $p\text{Confident Hits}/[p\text{Confident Hits}+p(\text{Confident False Alarms})]$) between young and older subjects. The accuracy of these high confidence recognition judgments approached ceiling in both groups, with values of .99 (SD=.02) and .98 (SD=.02) for young and older subjects, respectively.

Source Memory: Source memory performance is summarized in Table 2.4. To allow comparison with prior studies of the effects of age on source memory performance, which typically did not include either confidence ratings or a 'don't know' response option, an overall measure of source recollection (pSr) was estimated. The measure was derived from a single high-threshold model (Snodgrass and Corwin 1988; for example, see Gottlieb et al. 2010). To correct for the influence of guesses, source hit rates (collapsed over item and source confidence) were adjusted according to the formula, $p(\text{corrected source hit}) = [p(\text{source hit}) - .5(1 - p(\text{source don't know}))] / [1 - .5(1 - p(\text{source don't know}))]$. Replicating prior reports of age-related decrements in source accuracy, the adjusted source hit rate was significantly greater for the young group compared to the older group ($t_{40}=2.83$, $p<.01$), with values of .65 (SD=.13) and .51 (SD=.19), respectively).

As described below, to avoid confounding the variable of source accuracy with strength of item memory, we restricted analysis of fMRI subsequent source memory effects to those study items that went on to receive accurate, high confidence ‘old’ judgments. In addition, to minimize possible confounds between age group and source memory confidence, we further restricted the analyses to those source judgments that were both correct and made with high confidence. The source accuracies (the proportion of items receiving a confident old response that also received a correct, confident source judgment) associated with these critical trials were .67 (SD=.13) and .63 (SD=.16) for young and older subjects respectively; these means did not significantly differ.

2.3.3 fMRI Results

The subsequent memory analyses described below were based on contrasts derived from a mixed-effects 2x3 ANOVA model that incorporated factors of age group and subsequent memory condition (see Materials and Methods section).

We first present an analysis of the data from the young subjects alone, demonstrating that negative subsequent memory effects for item and source memory are localized to largely non-overlapping cortical regions. We then go on to describe the analyses of the data derived from both age groups. In these analyses, we sought evidence for both age-invariant negative subsequent memory effects, and effects that differed according to age.

Negative subsequent memory effects in the young group

In this preliminary set of analyses, we investigated whether negative subsequent memory effects for source and item encoding could be dissociated. This was accomplished by identifying each effect using the appropriate pairwise contrast (source hit < source miss, and source miss < item miss, each thresholded at $p < .001$ one-sided with a cluster extent threshold of 24 voxels), and exclusively masking it with the alternate contrast, thresholded at $p < .05$ (note that the more liberal the threshold of an exclusive mask, the more conservative is the procedure). As is evident in Figure 2.1b, and documented in Table 2.5, effects selective for the source contrast were localized to medial and bilateral prefrontal cortex (PFC), bilateral anterior insula/frontal operculum, the putamen and right temporo-parietal junction. By contrast, selective item effects were identified in medial parietal cortex, parts of the posterior cingulate, left temporo-parietal junction and ventromedial PFC (Figure 2.1a, Table 2.5). Thus, whereas the source effects were localized primarily to frontal regions, item effects were evident primarily in posterior regions of the cortex.

We also addressed the question of whether there were any regions where negative subsequent memory effects for item and source memory overlapped. When the contrasts were each thresholded at $p < .001$, no voxels survived the masking procedure. When the thresholds were lowered to $< .005$ (preserving the 24 voxel extent threshold; note that as the contrasts are non-orthogonal, it is not possible to estimate the conjoint significance level), two clusters were identified in right medial posterior cortex (see Figure 2.1c).

Age-invariant negative subsequent memory effects

Negative subsequent memory effects for item and source memory common to the two age groups were identified by separate contrasts for the item (item miss>item only) and source (source miss>source hit) effects respectively. Each contrast was thresholded at $p<.001$ with a cluster extent threshold of 24 contiguous voxels. The contrasts were exclusively masked by the appropriate group x subsequent memory interaction effect ($p<.05$, two-sided) to remove voxels where effects differed reliably according to age (cf. Morcom et al. 2003; Duverne et al. 2009; de Chastelaine et al. 2011). The masked contrasts identified the age-invariant negative subsequent memory effects summarized in Table 2.6 and briefly described below.

Item Memory: An age-invariant item effect was identified in a small region of right middle cingulate cortex (Figure 2.2a, Table 2.6).

Source Memory: Age-invariant negative source memory effects were identified in several regions, including left middle frontal gyrus, right middle cingulate cortex, bilateral insula/frontal operculum, and right supramarginal gyrus (see Figure 2.2b, Table 2.6). As is evident from the figure, the pattern of these effects across the brain resembles the pattern of selective negative subsequent memory effects for source memory illustrated in Figure 2.1b, with the exception of the inclusion of two posterior midline regions (that overlap the regions where item- and source effects co-existed in the young subjects). The mean across-region parameter effects for source hit and source miss study trials (along with the estimates for item miss trials, for illustrative purposes), are shown in Figure 2.2b.

Age-related differences in negative subsequent memory effects

We searched for regions where subsequent memory effects differed according to age by first computing separate group x subsequent memory interaction effects for item and source memory (thresholded at $p < .001$, two-sided). These contrasts identified regions where item or source effects differed with respect to age. To identify the voxels where reliable interaction effects were associated with negative subsequent memory effects in the young subjects, each F-contrast was inclusively masked with the respective negative subsequent memory contrast conducted on the young subjects' data only (thresholded at $p < .05$ one-sided).

Item Memory: Age-sensitive negative subsequent memory effects for item memory were identified in bilateral precuneus (overlapping one of the regions that demonstrated age-invariant negative source effects) and the left middle temporal gyrus (Figure 2.3, Table 2.7). To characterize these effects, we subjected the parameter estimates derived from these 4 regions to separate within-group ANOVAs, employing the factors of region and subsequent memory condition (item only vs. item miss). As would be expected in light of how the regions had been selected, the ANOVA for the young group revealed a reliable negative subsequent memory effect ($F_{(1,16)}=14.44$, $p < .005$) that did not vary across region ($p > .1$). By contrast, and consistent with the impression given by Figure 2.3, the ANOVA of the data from the older group revealed a significant *positive* effect ($F_{(1,24)}=6.28$, $p < .05$), that also did not vary significantly across region ($F < 1$).

Source memory: No voxels were identified where negative subsequent memory effects for source memory differed significantly with age at the pre-experimentally determined threshold.

Association of negative subsequent memory effects with memory performance

As noted in the Introduction, it has consistently been reported that the magnitude of negative subsequent memory effects in older subjects is positively correlated with memory performance (Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2011; Mormino et al. 2012). We therefore computed correlations between memory performance and the magnitude of negative subsequent memory effects in the regions identified in the foregoing analyses.

Item Memory: Regardless of whether item memory was estimated across confidence ratings (pHit-pFalse Alarms) or was restricted to those items given a confident recognition response, we were unable to identify any relationship, in either age group or across the combined groups, between performance and the magnitude of negative subsequent memory effects for items. This was the case for both the age-invariant effect in the right middle cingulate cortex (for pHit-pFA, $r=.217$, $p=.297$, and $r=.029$, $p=.856$ in the older and young subjects respectively), and with respect to the mean effects across the 4 regions demonstrating age-dependent effects (for pHit-pFA, $r= .372$, $p=.067$, and $r= -.181$, $p=.488$ for older and young subjects respectively).

Source Memory: For the purposes of these analyses we used as a measure of source performance the proportion of items receiving confident old judgments that also received a correct, confident source judgment (see *Behavioral Findings* above). Thus, the measure of source performance was derived from the same trials employed to estimate the fMRI effects.¹

Figure 2.4a illustrates the relationship between source memory performance and the across-region mean of the older subjects' negative subsequent source memory effects and source memory performance. Across the entire older sample, the correlation was .507 ($p < .005$, one-tailed). When an outlying subject (who had an across-region negative subsequent memory effect > 2 SDs above that of the across-region group mean) was omitted, the correlation increased substantially ($r = .592$, $p < .001$, one-tailed). We went on to compute separate correlations for each of the 8 regions listed in Table 2.6, omitting the outlier in each case. Significant correlations were evident in all but left and right insula regions ($r = .364$ -. $.564$, max $p < .05$, one-tailed). These correlations remained significant when the outlier subject was retained ($r = .355$ -. $.541$).

We repeated these analyses in the young group. The correlation between confident source accuracy and the negative source effects collapsed across regions approached significance ($r = .398$, $p < .06$, one-tailed). One region in left dorsolateral PFC (see Figure 2.2b) independently correlated significantly with performance ($r = .534$, $p < .05$, one-tailed).

¹ Results similar to those reported, but with weaker correlations, were obtained when either pSr or the simple probability of a correct source judgment (collapsed across item and source confidence) was used to index source performance.

In a final analysis we employed partial correlation to assess whether source performance was associated with the magnitude of negative subsequent memory effects for source memory (collapsed across region) in the combined samples after controlling for the effects of age. The partial r was .471 ($p < .005$, one-tailed; $r = .545$, $p < .001$, with the outlier removed) indicating that, as would be expected on the basis of the findings reported above, the relationship between negative subsequent source memory effects and source performance was independent of age (Figure 2.4b).

2.4 DISCUSSION

We investigated the effects of age on negative subsequent memory effects for item and source memory using a subsequent memory procedure that allowed item memory strength and source accuracy to be unconfounded, and the confidence of source memory judgments to be equated across age. In a preliminary analysis restricted to data from the young subjects, negative subsequent memory effects for item and source memory were found to be largely non-overlapping. Analyses of the data from both age-groups identified three classes of negative subsequent memory effect: age-invariant and age-dependent item effects, and age-invariant source effects. We did not identify any regions where there was a reliable age-related reduction in source effects, and the magnitude of the effects correlated with source memory performance in both age groups. Below, we discuss the implications of these findings and their possible relationship to previous reports of age-related differences in negative subsequent memory effects.

2.4.1 Behavioral findings

There was no difference between the age groups in study RTs, or in how study RT interacted with subsequent memory performance. Between-group differences in fMRI subsequent memory effects are therefore unlikely to be attributable to gross differences between the age groups in how efficiently the different classes of study items were processed. Study RTs did differ however as a function of subsequent memory condition, with both young and older subjects demonstrating the same pattern (item miss < source hit < source miss). The explanation for these RT effects is unclear. It is unlikely though that they contributed to any of the fMRI subsequent memory findings discussed below, since a subsidiary fMRI analysis conducted on study trials that had been matched for RT across the three subsequent memory conditions RT yielded qualitatively similar results.²

Consistent with numerous prior findings (e.g. McIntyre and Craik 1987; Schacter et al. 1991), young subjects demonstrated higher item and source memory performance than older subjects. As we discuss below, it is unlikely that these differences in memory performance can account for the age-related differences that were identified in fMRI subsequent memory effects. That said, it is important to note that recognition of items for which source memory failed (source misses) may have received differential support from recollection and familiarity in the two age groups. This possibility arises because recollection is more vulnerable to advancing age than familiarity (Howard et al. 2006; Prull et al. 2006; see

² The analysis equated study RTs in each subject by modeling a randomly-selected 5% of the slowest 'source miss' trials, and 10% of the fastest 'item miss' trials, as events of no interest.

Yonelinas 2002 for a review of early studies). Thus, although item memory strength (as indexed by response confidence and accuracy) was equated between the age groups, it is possible that source miss judgments in young subjects were more likely to be supported by recollection of episodic information from the study trial, albeit information that was non-diagnostic of source. Evidence in support of this possibility comes from a study by Toth and Parks (2006) in which it was demonstrated that ‘non-criterial recollection’ is indeed lower in older than in young subjects. This has implications for the interpretation of age-related differences in fMRI negative subsequent memory effects for item memory, as is discussed below.

2.4.2 fMRI findings

Negative subsequent memory effects in the young subjects

Before turning to the effects of age on negative subsequent memory effects, we briefly discuss the findings from the analysis of the young group alone. This revealed a clear dissociation between a largely posterior set of regions where only negative item effects were evident, and a second set, localized mainly in the PFC, anterior insula and putamen, where negative source, but not item, effects were identified. Two medial posterior regions demonstrated conjoint effects, such that negative item effects were enhanced when source encoding was successful.

As was noted in the Introduction, it is commonly held that negative subsequent memory effects reflect the benefit to encoding that ensues when default mode processes are

disengaged and cognitive resources are reallocated to the study event (e.g. Daselaar et al. 2004; Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2011). This account appears to work well in respect of the present negative subsequent memory effects for item memory. The effects were localized to regions typically considered to belong to the default mode network (see Buckner et al. 2008; Andrews-Hanna 2012 for reviews), and demonstrated the ‘task-negative’ stimulus-related activity – i.e. below-baseline parameter estimates – that is characteristic of the network (Raichle et al. 2001; Buckner et al. 2008).

By contrast, with the exception of the medial posterior regions where they overlapped with item effects, the present negative subsequent memory effects for source memory do not appear to reflect modulation of default mode activity. Several of the regions manifesting these effects, most notably, anterior insula and frontal operculum, are not considered components of the default mode network and, as is evident in Figure 2.2b, stimulus-related activity in these regions was task-positive (see Daselaar et al. 2004 for a prior report of negative subsequent memory effects in a task-positive region of the insula). Interestingly, the anterior insula and adjacent inferior frontal cortex are components of the ‘salience network’, which is held to be important for the initiation of cognitive control in response to behaviorally salient events (Seeley et al. 2007; Ham et al. 2013). This invites the speculation that the negative subsequent source memory effects in this region reflect the allocation of resources to salient aspects of a study episode that do not include information relevant to the later source judgment (see Otten and Rugg 2001, and Wagner and Davachi 2001, for earlier accounts of negative subsequent memory effects along similar lines).

To our knowledge, the present study is the first in which negative subsequent memory effects associated with successful item and source memory have been contrasted. Therefore it remains to be seen how far the findings generalize beyond the specific experimental procedures adopted here, for example, whether they extend to source memory tests for extrinsic rather than intrinsic contextual features.

Effects of age on negative subsequent memory effects

Item memory effects: Age-invariant negative subsequent memory effects for item memory were limited to a relatively small region of right middle cingulate cortex. This finding is reminiscent of a result from the study of Duverne et al. (2009), who also reported an age-invariant negative subsequent memory effect in posterior midline cortex, albeit in the precuneus rather than the cingulate. The present finding is mitigated however by the clear trend toward a larger middle cingulate effect in the young subjects (see Figure 2.2a). Moreover, this small age-invariant effect is overshadowed by the finding that negative item effects in medial posterior and left lateral temporal cortex were present in young subjects only, the effects in these regions demonstrating a statistically significant reversal in the older group (Figure 2.3). These findings are consistent with prior reports of age-related attenuation or reversal of negative subsequent memory effects for item memory (Morcom et al. 2003, Gutchess et al. 2005; Duverne et al. 2009; Mormino et al. 2012).

Although negative subsequent memory effects for item memory were largely absent in the older subjects, this appears to have had little impact on their recognition memory performance. Not only was there no relationship between the size of these effects and

recognition performance, but a subsidiary analysis revealed that negative effects were absent even in a sub-set of 16 older subjects selected so that their mean item memory did not differ significantly from that of the young group (Hit-FA of .80 in both groups). As in the older group as a whole, the effects in these high-performing subjects were not only attenuated, but reversed ($p < .05$, two-tailed). A similar result was reported by Duverne et al. (2009), who described non-significant (rather than reversed) negative subsequent memory effects in an older sub-group whose recognition memory performance was matched with that of a young sample.

Clearly, reliable negative subsequent memory effects for item memory are not necessary for older individuals to attain levels of memory performance equivalent to those in young subjects. What, then, is the functional significance of these effects? As was noted above, the effects in the young sample were localized mainly to regions belonging to the default mode network. Thus, the attenuation of negative item effects in the older group might be a reflection of a more general failure to disengage the network in response to a stimulus event to the same extent as young individuals (e.g. Lustig et al. 2003; Grady et al. 2006). This does not, however, explain why failure to disengage default mode processes seemingly had no impact on item memory performance.

One possible account of the dissociation between negative item effects and item memory performance in older subjects arises from the possibility, discussed previously, that older and young subjects differed in the likelihood that they recollected details of the study episode that were non-diagnostic of source information (non-criterial recollection). The

account is predicated on two assumptions. First, that in older subjects, recognition memory for source miss items was largely familiarity-driven, but that recognition of these items in young subjects was supported by a combination of familiarity and non-criterial recollection. Second, that negative subsequent memory effects for item memory reflect encoding operations that benefit subsequent recollection, but do not impact familiarity. Given these assumptions, the age-related dissociation in negative subsequent memory effects for item memory can be attributed to the failure of older subjects to encode non-criterial information, and, concomitantly, to disengage default processes that facilitate encoding of such information.

An alternative explanation for the lack of correspondence in older subjects between negative subsequent memory effects for item memory and performance is suggested by the findings of a recent event-related potential (ERP) study. Wang et al. (2012b; see Duarte et al. 2006 for similar findings) reported that a putative ERP correlate of familiarity-driven recognition memory was undetectable in older subjects, including a sub-group in whom familiarity-strength was matched with that of a group of young subjects in whom the ERP correlate was highly reliable. Wang et al. (2012) proposed that their findings might indicate that familiarity-driven recognition memory is supported by multiple memory signals, not all of which are reflected in the ERP effect. They further proposed that the different familiarity signals decline differentially with advancing age, causing the dissociation they reported between a putative neural correlate of familiarity and familiarity-driven recognition memory. Applying the same argument here, the proposal would be that whereas source misses in both older and young individuals were supported largely by familiarity, the familiarity signal that

depended upon encoding processes reflected in negative item subsequent memory effects was minimal in older subjects, in whom familiarity was supported by encoding processes uncorrelated with negative subsequent memory effects.

Arbitrating between these (and other) accounts will not be possible until more evidence is available about the relationship between negative subsequent memory effects and familiarity- and recollection-based recognition memory. Also, it should be noted that while these accounts might explain why older subjects can demonstrate seemingly intact memory performance in the face of attenuated or absent negative subsequent memory effects, they do not explain why the effects sometimes reverse, as in the present case and some previous reports (Morcom et al. 2003; Duverne et al. 2009). We can offer no explanation for this puzzling finding.

Source memory effects: In striking contrast to negative subsequent memory effects for item memory, we did not identify any regions where negative source effects varied according to age. Furthermore, reminiscent of prior findings (de Chastelaine et al. 2011; Miller et al. 2008), the magnitude of negative source effects correlated with source memory performance both in older subjects and in the combined older and young samples. The findings from the separate analysis of the young subjects indicate that negative source memory effects dissociate according to whether or not they co-exist with item memory effects. We discuss the finding of age-invariant negative subsequent memory effects for source memory in light of this dissociation.

The negative source effects identified in posterior midline cortex (see Figure 2.2b) are in the same default mode regions where source and item effects overlapped in the analyses of the data from the young subjects (cf. Figure 2.1c). The more posterior of these regions also overlaps with where negative item effects dissociated with age (see Figure 2.1a). Therefore the absence in older subjects of negative subsequent memory effects for item memory in this region does not reflect an incapacity to disengage the region in service of episodic encoding: relative to source miss study trials, source hit trials were associated with equivalent levels of disengagement in the two age groups. This finding is consistent with the proposal that, in at least some components of the default mode network, negative subsequent memory effects reflect processes that facilitate later recollection of the study episode. The proposal receives further support from the finding that the magnitude of negative source effects in the aforementioned medial posterior regions correlated with source memory performance across age groups (controlling for age, partial $r=.368$ ($p<.01$, one-tailed)). The proposal is also consistent with prior findings that negative subsequent memory effects in older subjects correlate with performance on other memory tests that likely depend heavily on recollection (de Chastelaine et al. 2011; Miller et al. 2008). In short, despite the more restricted modulation of default mode activity that is apparent in older individuals relative to their young counterparts (Lustig et al. 2003; Grady et al. 2006), the relationship between successful episodic encoding and disengagement of default processing does not appear to change with age.

If the foregoing account is correct, why have prior studies that employed subsequent memory tests that were dependent on recollection reported age-related attenuation of

negative subsequent memory effects? We conjecture that this is because, unlike in the present study, the memory tests employed in previous studies did not allow strength of recollection to be equated across the age groups. For example, in the study of de Chastelaine et al. (2011), associative recognition performance in older subjects was markedly lower than it was in the young group, indicative of an age-related difference in the strength of the memory signal supporting the associative recognition judgments. Thus, the subsequent memory effects were likely associated with the encoding of information that (on average) supported strong and weak recollection-based judgments in younger and older subjects respectively. According to this account, had de Chastelaine et al. (2011) been able to restrict negative subsequent memory effects to study pairs that went on to receive highly confident recognition judgments, age-related differences in the magnitude of the effects would have been much diminished.

As was noted previously, age-invariant negative subsequent memory effects for source memory were mainly localized to frontal ‘task-positive’ regions that would usually be considered to fall outside of the default mode network. It has been suggested that enhanced task-positive responses to ‘forgotten’ items are indicative of the engagement of processes that interfere or compete for resources with processes that support effective encoding (Daselaar et al. 2004). Regardless of the validity of this proposal, the frontal negative source effects appear to be as closely associated with successful episodic encoding as those in the putative default mode regions that were discussed above: collapsed across regions and age group, the partial correlation (controlling for age) between the magnitude of these effects and source memory performance was .446 ($p < .005$, one-tailed). As we have already discussed, it is

possible that these frontal effects, or at least those localized to the anterior insula and adjacent prefrontal cortex, reflect the allocation of cognitive resources to salient, but mnemonically unhelpful, aspects of the study episode. Whether or not this turns out to be a valid account of these effects, it is clear they are as closely linked to the successful encoding of contextual information in older individuals as they are in young subjects. Thus, as in the case of the negative source effects localized to putative default mode regions, the present findings suggest that the relationship between negative frontal effects and source memory performance does not vary with age.

2.4.3 Concluding comments

Age-related attenuation of negative subsequent memory effects is one of the most consistent findings in studies investigating the effects of age on the neural correlates of episodic encoding. The present study is no exception: relative to study items that failed to be recognized on a later memory test, negative subsequent memory effects in regions of the default mode network were attenuated in older subjects both for confidently recognized items that attracted a correct source memory judgment, and items that did not. Crucially, though, the negative effects that predicted whether memory for an item's encoding context would be strong and accurate, or would fail, did not differ with age and demonstrated the same relationship with memory performance in the two age groups. We conclude that the negative subsequent memory effects for source memory identified here reflect modulations of stimulus-related activity that support successful episodic encoding and that, when the strength of subsequent source memory is matched, that these effects are age-invariant. It

remains to be seen whether, when strength of item and contextual memory are controlled as here, the present findings generalize to other study materials and subsequent memory tests.

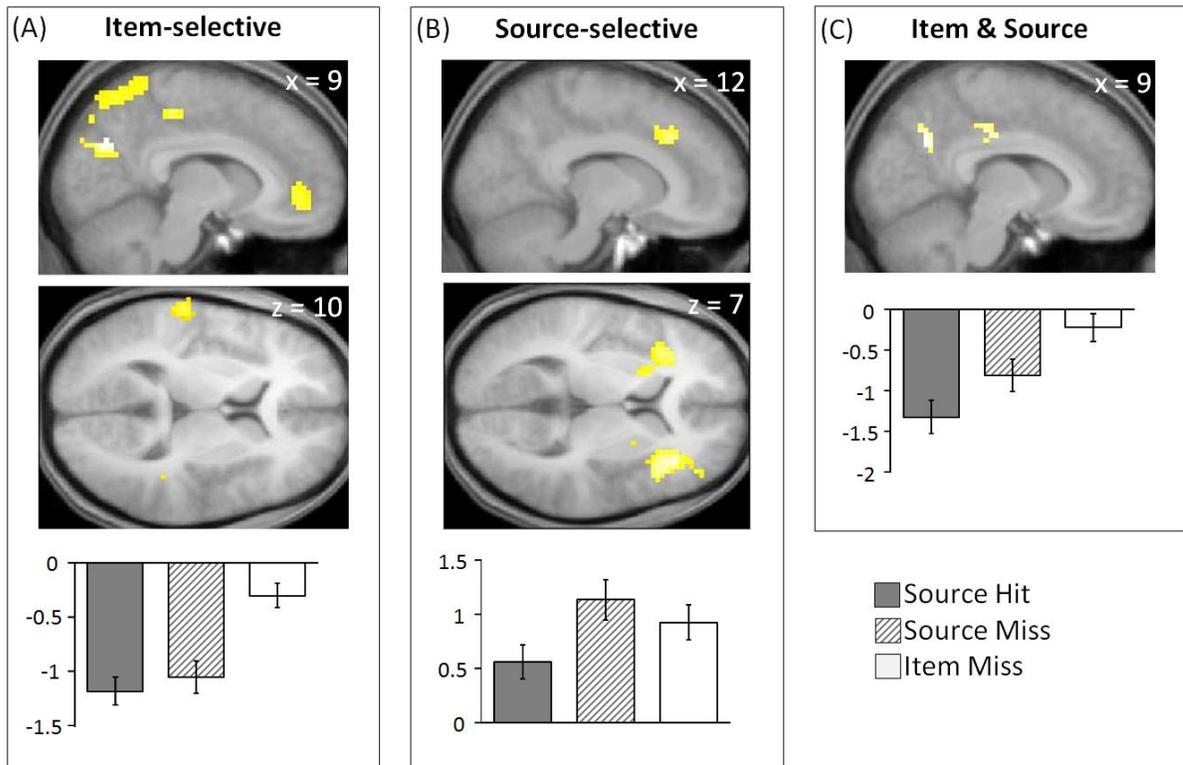


Figure 2.1 Negative subsequent memory effects in young subjects. Top: Regions demonstrating (A) negative subsequent memory effects for item, but not source, memory (left supramarginal gyrus, and right superior temporal gyrus not shown) (B) negative subsequent memory effects for source, but not item, memory (right superior temporal gyrus not shown) and (C) negative subsequent memory effects for both item and source memory (averaged across item and source peaks) in young subjects. Effects are shown on sections of young subjects' mean normalized structural image. Bottom: Average parameter estimates (arbitrary units) for each response category.

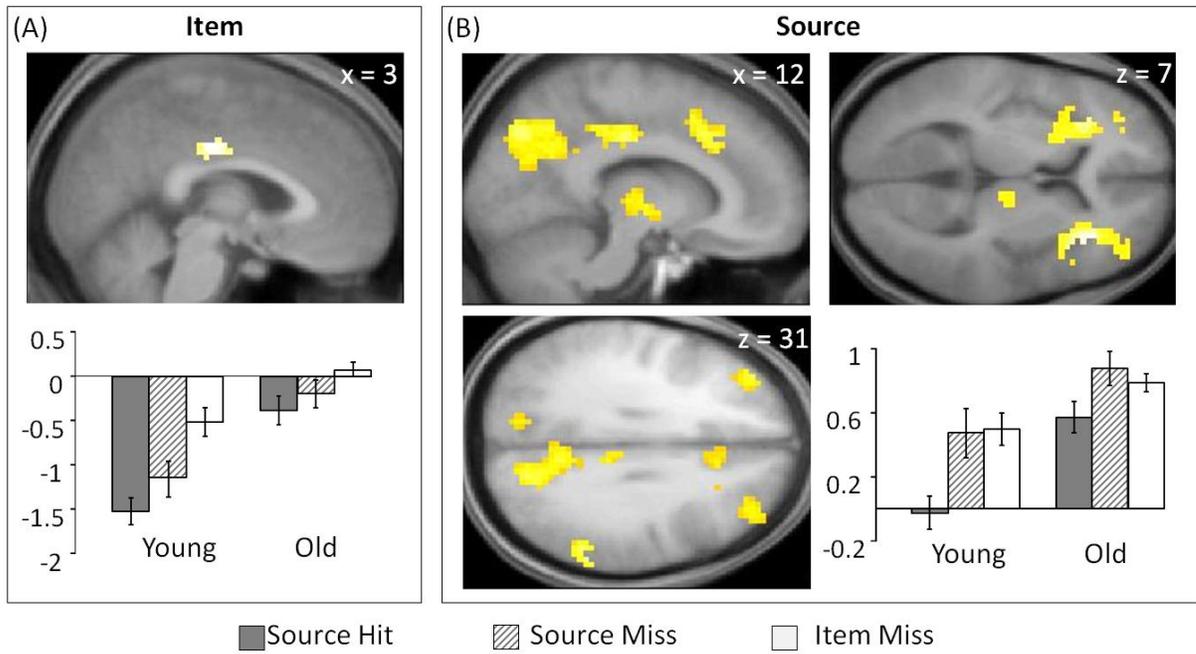


Figure 2.2 Regions demonstrating age-invariant negative subsequent memory effects for item memory (A) and source memory (B) effects. Bar charts depict mean across-region parameter estimates (arbitrary units).

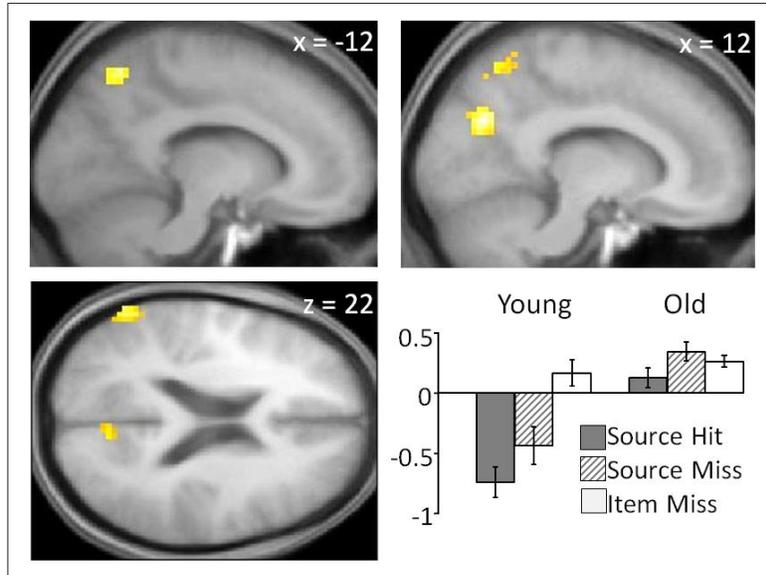


Figure 2.3. Regions demonstrating age-related differences in negative item subsequent memory effects. Bar chart depicts mean across-region parameter estimates (arbitrary units).

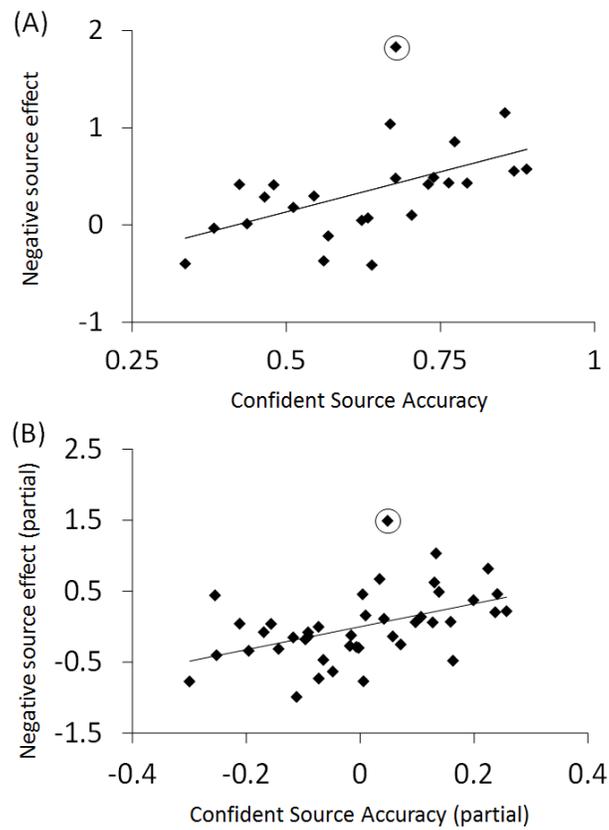


Figure 2.4. Scatterplots illustrating the relationship between negative subsequent memory effects (in arbitrary units) for source memory and the proportion of confidently recognized old items given an accurate, confident source judgment. The subsequent memory effects are averaged across the eight regions listed in Table 2.6 that demonstrate age-invariant negative effects in older subjects. (A) Older subjects; (B) young and older subjects (residual scores after controlling for age). Outlying older subject circled (see text).

Table 2.1 Demographic and neuropsychological data (mean, SD and range) for young and older subjects

	Young			Old		
	Mean	SD	Range	Mean	SD	Range
Age	19.7	2.2	18-27	67.1	3.6	62-74
Years of education**	14.2	1.8	13-20	16.6	2.3	12-22
Mini Mental State Examination	29.5	1.0	26-30	28.8	1.2	27-30
CVLT composite recall score**	13.6	1.8	10-16	12.0	2.3	8-16
CVLT recognition hits	15.2	0.8	14-16	14.8	1.3	12-16
CVLT recognition false positives**	0.6	1.1	0-4	1.7	1.0	0-7
WMS Logical Memory II composite score	28.6	6.0	20-39	26.4	5.0	15-36
Forward/Backward Digit Span	18.4	3.8	12-25	17.8	3.5	11-28
Digit/Symbol Substitution Test***	69.1	11.3	54-86	50.6	8.0	35-68
Trail Making Test A***	18.9	3.8	13-26	24.7	5.0	15-37
Trail Making Test B**	46.4	14.5	26-83	65.7	20.2	37-98
Letter Fluency	42.2	10.2	31-69	44.6	11.4	22-64
Category Fluency	24.2	4.1	16-30	21.8	5.3	11-36
WTAR FSIQ	110.4	4.9	101-119	111.2	4.3	101-117

Note: CVLT=California Verbal Learning Test

CVLT composite recall score=averaged scores from CVLT cued and free recall for both short and long delay.

WMS=Wechsler Memory Scale

FSIQ=Full Scale Intelligence Quotient

*p<0.05, **p<0.01, ***p<0.001, two-tailed t-tests

Table 2.2
 Mean study reaction times (ms) segregated by subsequent memory response (\pm SD)

	CO	UO	DK	UN	CN
Item					
Young	1737 (276)	1717 (304)	1687 (370)	1641 (309)	1736 (310)
Old	1799 (360)	1801 (474)	1779 (407)	1710 (383)	1750 (396)
	CC	UC	DK	UI	CI
Source					
Young	1734 (273)	1746 (299)	1767 (265)	1771 (351)	1751 (347)
Old	1790 (364)	1818 (408)	1798 (550)	1798 (362)	1848 (419)

Note: Study reaction times for source memory restricted to encoding trials later endorsed as confidently old. Response abbreviations correspond to the following: CO, confident old; UO, unconfident old; DK, don't know; UN, unconfident new; CN, confident new; CC, confident correct; UC, unconfident correct; UI, unconfident incorrect; CI, confident incorrect.

Table 2.3
 Mean proportions of item memory judgments for old and new trials by response type (\pm SD)

	CO	UO	DK	UN	CN
Young					
Old	.76 (.09)	.08 (.05)	.03 (.03)	.07 (.05)	.06 (.06)
New	.01 (.02)	.01 (.02)	.04 (.06)	.15 (.18)	.78 (.23)
Old					
Old	.68 (.15)	.07 (.07)	.03 (.06)	.08 (.08)	.13 (.10)
New	.02 (.02)	.02 (.04)	.03 (.05)	.18 (.24)	.75 (.27)

Note: Response abbreviations correspond to the following: CO, confident old; UO, unconfident old; DK, don't know; UN, unconfident new; CN, confident new.

Table 2.4
 Mean proportions of source judgments for confidently and unconfidently recognized study items

	Confident Source Correct	Unconfiden t Source Correct	Don't know Source	Unconfiden t Source Incorrect	Confident Source Incorrect
Young					
Confident Old	.67 (.13)	.17 (.13)	.03 (.04)	.06 (.04)	.07 (.06)
Unconfident Old	.20 (.18)	.41 (.27)	.11 (.14)	.20 (.13)	.08 (.14)
Old					
Confident Old	.63 (.16)	.14 (.12)	.03 (.04)	.06 (.07)	.15 (.09)
Unconfident Old	.15 (.15)	.47 (.22)	.06 (.10)	.26 (.22)	.07 (.13)

Table 2.5

Young subjects: negative subsequent memory effects for item and source memory

	Coordinates			Peak Z	Number of above- threshold voxels	Region
	x	y	z			
Item	-63	-25	10	4.00	56	L temporoparietal junction
	-63	-43	37	4.41	154	L supramarginal gyrus
	9	47	1	3.90	73	R middle orbital gyrus
						R middle/posterior cingulate cortex
	3	-28	49	4.18	86	
	45	-40	34	3.72	47	R temporoparietal junction
	9	-70	31	5.04	443	R precuneus
Source	-33	23	7	4.04	169	L insula
	36	29	7	4.72	253	R insula
	12	26	37	4.11	138	R anterior cingulate cortex
	57	-43	28	4.57	57	R temporoparietal junction
Item & Source (item peaks)	6	-22	40	3.87	24	R middle cingulate cortex
	12	-64	37	4.12	50	R precuneus
Item & Source (source peaks)	3	-25	31	3.19	24	R middle cingulate cortex
	9	-58	31	3.55	50	R precuneus

Table 2.6

Age-invariant negative subsequent memory effects

	Coordinates			Peak Z (young; old)	Number of above- threshold voxels	Region
	x	y	z			
Item	3	-19	37	3.96 (3.56; 2.01)	33	R middle cingulate cortex
Source	-33	44	7	3.47 (2.52; 2.46)	25	L middle frontal gyrus
	-36	41	25	3.95 (3.60; 1.94)	71	L middle frontal gyrus
	-30	29	7	4.41 (3.81; 2.45)	207	L insula/frontal operculum
	33	32	7	5.08 (4.24; 3.05)	480	R insula/frontal operculum
	6	14	46	4.75 (3.69; 3.17)	355	R anterior cingulate cortex
	12	-22	40	4.20 (3.43; 2.56)	137	R middle/posterior cingulate cortex
	63	-43	31	4.26 (3.98; 1.99)	105	R supramarginal gyrus
	12	-76	40	4.25 (2.85; 3.33)	504	R precuneus/posterior cingulate cortex

Table 2.7
Age-dependent negative subsequent memory effects

	Coordinates			Peak Z	Number of above- threshold voxels	Region
	x	y	z			
Item	-60	-61	22	3.84	41	L temporoparietal junction
	-12	-61	58	3.88	46	L precuneus
	15	-58	55	3.56	30	R precuneus
	12	-67	31	4.24	168	R precuneus

CHAPTER THREE

EFFECTS OF AGE ON POSITIVE SUBSEQUENT MEMORY EFFECTS ASSOCIATED WITH THE ENCODING OF NON-VERBAL ITEMS.

3.1 Introduction

The present chapter reports data from the same fMRI experiment as Chapter 2. As mentioned in the Chapter 1 (Section 1.5.2), one consistent finding within the neuroimaging literature has been the finding of a more bilateral pattern of memory-related activity in older compared to younger individuals (e.g. Rosen et al. 2002; Cabeza et al. 2003; Morcom et al. 2003; Grady et al. 2005; Fernandes et al. 2006; van der Veen et al. 2006; Duverne et al. 2008; Bangen et al. 2012). This phenomenon of greater levels of frontal activity in older adults – sometimes termed ‘age-related over-recruitment’ – is thought to possibly reflect engagement of compensatory or adaptive processes to maintain cognitive function in the context of healthy aging (Cabeza 2002; Davis et al. 2008; Bangen et al. 2012). An alternate account suggests that age-related changes in neural function have a detrimental impact on memory performance, and reflect possible age-related reductions in transcallosal inhibition or cortical differentiation of function (Li and Lindenber 1999; Logan et al. 2002).

In order to adjudicate between these accounts, cross-sectional studies fMRI studies of memory encoding have employed the subsequent memory procedure (Paller and Wagner 2002) and compared regions demonstrating subsequent memory effects – or difference in neural activity due to later memory – in young and older subjects. Studies of memory

encoding using verbal materials have found that positive subsequent memory effects (greater activity for later remembered compared to later forgotten study items) in PFC are left-lateralized in younger subjects and more bilaterally distributed in older subjects (Morcom et al. 2003; Duverne et al. 2008). While the engagement of left PFC in the encoding of verbal stimuli has been shown to be positively correlated with memory performance in older subjects (de Chastelaine et al. 2011), the engagement of right PFC in older subjects has been associated with poorer memory performance (Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2011).

It is unclear, however, whether this negative relationship between right frontal subsequent memory effects and performance exists for encoding of non-verbal items. The finding of increased right prefrontal engagement in encoding of verbal materials prompted Gutchess et al. (2005) to investigate whether this finding extended to encoding of *non*-verbal materials, which have been previously shown to produce bilateral prefrontal patterns of activity in young subjects (Golby et al. 2001; Kelly et al. 1998). Gutchess et al. (2005) reported that, when comparing later remembered scenes versus later forgotten scenes, no significant laterality differences in subsequent memory effects were observed for inferior frontal regions between younger and older subjects. Other studies using scenes have also reported bilateral patterns of positive subsequent memory effects in PFC across younger and older subjects (Mormino et al. 2012). It is not known, however, whether older adults' engagement of right PFC in circumstances where younger adults *also* demonstrate bilateral PFC effects (such as in the case of encoding non-verbal stimuli) is associated with relatively poor memory performance.

The primary motivation of the present study was to investigate the effects of age on frontal subsequent memory effects using pictorial materials. We employed a source memory task in order to create a paradigm where we could additionally ask about the neural correlates of the successful formation of item-context associations in older and younger subjects. By using a task in which we only looked at memory for study pictures that were associated with accurate and high confidence judgments, we were able to reproduce the same circumstances under which previous studies of verbal memory encoding (Morcom et al. 2003; Duverne et al. 2008) have investigated single item encoding as a function of age. We were able to gain added value from the study by including our source memory manipulation and asking whether there were any regions that were sensitive to item-context encoding, and whether these effects differed as a function of age.

3.2 Materials and Methods

Materials and methods pertaining to the data reported in the present chapter can be found in Chapter 2 (which reports data from the same fMRI experiment), Section 2.2 (2.2.1 Subjects and neuropsychological testing, 2.2.2 Stimulus materials, 2.2.3 Experimental tasks and procedures, 2.2.4 MRI Data Acquisition, 2.2.5 MRI Data Analysis). Additionally, the present data analyzes diffusion tensor images, which were acquired with a single-shot EPI sequence (48 directions, 60 transverse slices, 2mm thick, no gap, matrix size 112-109, TR 12350ms, TE 71ms; flip angle 70°, b 1000s/mm², $1xb=0$).

3.2.1 DTI Data Analysis

DTI data were analyzed using the DTIstudio package, which calculates diffusion anisotropy by applying nonrigid registration to correct for motion and eddy current-related deformations (Jiang et al. 2006). Fractional Anisotropy (FA) maps were calculated from the tensor parameters, with FA values scaled from 0 to 1, representing isotropic diffusion and maximal anisotropy, respectively. FA maps were visualized in MRICron, with minimum contrast value set to .2 and maximum contrast value set to .5. DTI images were reoriented parallel to the anterior commissure-posterior commissure (AC-PC) line but not normalized. For each subject, the middle axial slice across the genu (mean number of slices: 8; range: 4-12) and splenium (mean number of slices: 7; range: 4-15) was used to place a 3mm-radius spherical ROI in the center of the anterior and posterior corpus callosum, respectively. Although FA values extracted from 3-mm radius spheres were used for the present analyses, these values correlated highly with FA measurements from 5-mm radius spheres (genu: $r=.940$, splenium: $r=.679$; $ps<.001$) as well as FA values derived from manual tracing of the full extent of each region (genu: $r=.783$, splenium: $r=.505$; $ps<.001$).

3.3 RESULTS

Neuropsychological data and behavioral results pertaining to the present chapter can be found in Chapter 2, Sections 2.3.1 and 2.3.2, respectively.

3.3.1 DTI Data

Mean FA values within 3mm-radius spheres in the anterior and posterior corpus callosum are presented in Figure 1. ANOVA (factors of age and callosal region) revealed a main effect of age ($F_{1,40}=17.75$, $p<.001$) that was modified by an age x region interaction ($F_{1,40}=13.08$, $p<.005$). The main effect reflected higher FA (and hence higher microstructural integrity) in the young subjects. The interaction arose because the age effect was greater in the anterior (mean FA of .79 and .71 for young and older subjects, respectively; $F_{1,40}=28.72$, $p<.001$) than in the posterior (means of .83 vs. .82; $F_{1,40}<1$) corpus callosum, consistent with numerous prior reports (e.g. Sullivan and Pfefferbaum 2006).

In light of a prior report that anterior callosal FA and memory performance were positively correlated in older adults (Persson et al. 2006), we computed separate correlations between anterior/posterior callosal FA and item/source memory across subjects. Across all subjects, controlling for age, there was no significant relationship between anterior callosal FA and item or source memory performance. A significant relationship was observed, however, between posterior callosal FA and source (but not item) memory performance ($r=.329$, $p<.05$).

We then went on to compute separate correlations in the older group. There was no significant relationship between anterior callosal FA and item or source memory performance. However, a significant relationship between posterior callosal FA and source memory performance was observed ($r=.427$, $p<.05$).

Additionally, in light of prior reports demonstrating age-related differences in processing speed being mediated by differences in white matter integrity, we computed the relationship between callosal FA and study RTs. Across all subjects, controlling for age, there was a significant negative relationship between study RTs and anterior, but not posterior, callosal FA ($r = -.329$, $p < .05$). Thus, faster study reaction times were associated with greater anterior callosal FA. We went on to compute the relationship between study RTs and callosal FA in the older group, and found a similar negative relationship with anterior, but not posterior, FA ($r = -.560$, $p < .001$).

3.3.2 fMRI Results

The subsequent memory analyses described below were based on contrasts derived from a mixed-effects 2x3 ANOVA model that incorporated factors of age group and subsequent memory condition (see Methods section from Chapter 2, Section 2.2).

Age-invariant subsequent memory effects

We identified areas demonstrating subsequent item and source memory effects common to the two age groups by the separate contrasts for item (source miss > item miss) and source (source hit > source miss) effects respectively ($p < .001$). The contrasts were exclusively masked by the appropriate group x subsequent memory interaction effect ($p < .05$, two-sided) to remove voxels where effects differed reliably according to age (cf. Morcom et al. 2003; Duverne et al. 2009; de Chastelaine et al. 2011). Note that the more liberal the threshold of an exclusive mask, the more conservative the masking procedure. The masked

contrasts identified the age-invariant negative subsequent memory effects summarized in Table 3.5 and described below.

Item Memory: Age-invariant subsequent item memory effects were identified in several regions, including bilateral IFG, and bilateral occipital gyrus (Figure 2, Table 3.4).

Source Memory: At the pre-experimental threshold, no regions were identified that demonstrated age-invariant subsequent source memory effects. As noted in the Introduction (Section 3.1), we expected to find effects in the medial temporal lobe. When we reduced the threshold to $p < .01$, a 26-voxel cluster demonstrating age-invariant subsequent source memory effects was identified in the left hippocampus (Figure 3, Table 3.6).

Age-related differences in subsequent memory effects

We searched for regions where subsequent memory effects differed according to age by first computing separate group \times subsequent memory interaction effects for item and source memory (thresholded at $p < .001$, two-sided). These contrasts identified regions where item or source effects differed with respect to age.

Since we focused on regions demonstrating positive subsequent memory effects, we exclusively masked the separate group \times subsequent memory interaction contrasts with the respective negative subsequent memory contrast conducted on the young subjects' data only (thresholded at $p < .05$ one-sided). No voxels could be identified where subsequent item or

subsequent source memory effects differed significantly with age at the pre-experimentally determined threshold.

Frontal Subsequent Memory Effects

To further characterize the effects of age on left and right frontal subsequent memory effects in an unbiased manner, we performed an ROI analysis using the same approach as that employed in previous studies (Duverne et al. 2009; Chastelaine et al. 2011).

Left and homotopic right IFG

Peak voxels demonstrating a main subsequent memory effect across both age groups in dorsal [-45 29 7] and ventral [-36 32 -11] left IFG were identified from the directional contrast for the main effect of subsequent memory ((source hit+source miss)>item miss) in the omnibus ANOVA. In order to sample activity along the entire extent of the IFG, the locus of a voxel in left middle IFG was obtained by averaging the coordinates of the dorsal and ventral peaks ([-39 29 -2]). We then extracted mean parameter estimates within 5mm radius spheres around each of the three voxels and from homotopic ROIs in the right hemisphere (dorsal: [45 29 7]; middle: [39 29 -2]; ventral: [-36 32 -11]).

Preliminary analyses demonstrated that both source hit and source miss items independently demonstrated reliable subsequent memory effects relative to item misses ($F_{(1,40)}=24.13$, $p<.0001$; $F_{(1,40)}=29.08$, $p<.0001$, respectively), but that IFG responses to these two response categories did not differ reliably ($F_{(1,40)}=3.58$, $p=.066$). We therefore averaged subsequent item and subsequent source memory effects to produce a more stable estimate of subsequent memory effects, hereafter referred to as the ‘subsequent memory effect’.

ANOVA employing factors of age group, subsequent memory, and hemisphere revealed main effects of region and subsequent memory but no effect including the factor of age group. There was a significant interaction between hemisphere and subsequent memory ($F_{(1,40)}=15.33$, $p<.001$), with larger effects in the left hemisphere compared to the right. Follow-up ANOVAs were separately performed for left and right hemispheres and demonstrated that subsequent memory effects were reliable in both left and right hemispheres ($F_{(1,40)}=50.20$, $p<.001$; $F_{(1,40)}=19.82$, $p<.001$, respectively), with no significant age x subsequent memory interaction in either hemisphere. There was also an interaction between region and overall subsequent memory ($F_{(1,8,72,5)}=3.98$, $p<.05$), with follow-up analyses revealing greater subsequent memory effects in dorsal compared to ventral IFG. Consistent with our prior voxel-wise analyses, these ROI analyses failed to demonstrate an influence of age on the magnitude or lateralization of frontal subsequent memory effects.

Right and homotopic left IFG

We repeated the above analyses for peak voxels demonstrating a subsequent memory effect in right IFG (dorsal: [48 14 25]; middle: [54 35 10]; ventral: [33 32 -11]), along with homotopic ROIs in the left hemisphere (dorsal: [-48 14 25]; middle: [-54 35 10]; ventral: [-33 32 -11]). ANOVA employing factors of age group, subsequent memory, and hemisphere similarly revealed main effects of region and subsequent memory but no effect including the factor of age group. Unlike the above analyses using ROIs identified from left IFG regions, there was no significant interaction between hemisphere and subsequent memory ($F_{(1,40)}<1$). There was, however, an interaction between region and subsequent memory effect

($F_{(2,78.2)}=5.29$, $p<.01$), with follow-up analyses revealing greater subsequent memory effects in ventral compared to dorsal regions.

Relationship between Frontal Effects and Callosal Integrity

As note in the Introduction, right prefrontal recruitment has been hypothesized to partially compensate for the functional decline in left frontal cortex (de Chastelaine et al. 2011). That is, although prior reports have proposed that right frontal over-recruitment is a consequence of a weakening of transcallosal inhibition due to compromised callosal integrity (Logan et al. 2002; Persson et al. 2006; Sullivan and Pfefferbaum 2006), it appears that recruitment of right frontal cortex – at least in the case of a relational, verbal study task – is facilitated by relatively *higher* callosal integrity (de Chastelaine et al. 2011). We therefore investigated whether, in older adults, callosal integrity was significantly correlated with frontal subsequent memory effects in our study task which utilized non-verbal materials.

Left IFG

Across older subjects, the relationship between callosal FA and mean subsequent memory effects in left IFG regions was not significant when ROIs were derived from peak left IFG regions. However, when ROIs were derived from homotopic left IFG regions, mean left frontal subsequent memory effects in older subjects were positive correlated with both anterior and posterior FA ($r=.418$ and $.449$, respectively; $ps<.05$). The scatterplot for these correlations across left IFG regions derived from right IFG peaks are depicted in Figure 4a (top).

We went on to compute, controlling for age, the correlation between mean left frontal subsequent memory effects and FA across both groups. No significant relationships between anterior or posterior FA and mean left frontal subsequent memory effects were found across both age groups when ROIs were derived from peak left IFG regions. In left IFG regions derived from right IFG peaks, however, the relationship was significant for anterior FA (partial $r=.399$, $p<.05$) but not posterior FA (partial $r=.295$, $p=.061$). The partial plot for this correlation is depicted in Figure 4a (bottom).

Right IFG

Across older subjects, the mean magnitude of right frontal overall subsequent item memory effects across the ROIs derived from peak right IFG regions was positively correlated with posterior FA ($r=.488$, $p<.05$, two-tailed) but not anterior FA values. The scatterplots of FA values and mean right frontal overall subsequent memory effects is illustrated in Figure 4b (top). The relationship between right frontal subsequent memory effects and posterior FA (but not anterior FA) was also significant when ROIs in right IFG were derived from peak voxels in left IFG regions ($r=.438$, $p<.05$).

Across both age groups, when controlling for age, the partial correlation between right frontal overall subsequent memory effects from peak right IFG regions and FA was significant for anterior FA (partial $r=.391$, $p<.05$) but not posterior FA (partial $r=.295$, $p=.061$). The partial plot is depicted in Figure 4b (bottom). No significant correlations with

FA were found across both age groups when ROIs in right IFG were derived from left peak IFG regions.

Relationship between Frontal Effects and Memory Performance

As noted previously (Section 1.5.2; Section 3.1), the magnitude of left frontal subsequent memory effects has been previously shown to correlate positively with memory performance while the magnitude of right frontal subsequent memory effects has been associated with poorer performance in older subjects (de Chastelaine et al. 2011). We therefore investigated the relationship between memory performance and the magnitude of frontal subsequent memory effects across IFG regions identified in the foregoing analyses. For the purpose of these analyses we employed memory measures that were derived from the same trials used to estimate fMRI effects. For item memory, we calculated a ‘confident item memory’ measure by subtracting confident false alarms from confident item hits. For source memory, we used as a measure of source performance the proportion of items receiving confident old judgments that also received a confident and correct source response (hereafter termed ‘confident source accuracy’).

Left IFG

Across both age groups, controlling for age, the mean magnitude of frontal subsequent memory effects in left ROIs (derived from either peak left or peak right IFG regions) did not significantly correlate with confident item memory or confident source accuracy. However, when separate correlations for each of the ROIs in dorsal, middle, and ventral IFG were

computed in left IFG regions (derived from left and right IFG peaks), there was a significant relationship between left frontal subsequent memory effects and both confident item memory and confident source accuracy in both of the neighboring ventral left IFG regions ($r=.362-.370$; $p<.05$). The scatterplots depicting these correlations are illustrated in Figure 3.5a.

We went on to compute separate correlations in young and older groups separately. There was no significant relationship in either group between subsequent memory effects in left IFG regions (both collapsed across region, as well as for each region separately) and confident item memory or confident source accuracy.

Right IFG

Across both age groups, when controlling for age, the magnitude of right frontal subsequent memory effects (collapsed across peak right IFG regions) was not significantly correlated with confident item memory, although there was a positive trend for confident source accuracy (partial $r=.304$, $p=.054$). There was no significant relationship with either memory measure when ROIs in right IFG were derived from peak left IFG regions.

However, when separate correlations were computed for ROIs in dorsal, middle, and ventral right IFG, there was a significant relationship between right frontal subsequent memory effects and both confident item memory and confident source accuracy in the dorsal right IFG region ($r=.341$ and $.330$, respectively; $p<.05$). The scatterplots depicting these relationships are illustrated in Figure 3.5b.

We went on to compute correlations in young and older groups separately. There was no significant relationship in either group between frontal subsequent memory effects in right IFG regions (both collapsed across region, as well as for each region separately) and confident item memory or confident source accuracy.

Multiple Regression Analysis

The foregoing analyses indicate that, across both groups (when controlling for age), anterior callosal FA, confident item memory, and confident source accuracy each correlated with the magnitude of left and right frontal subsequent memory effects, at least in left ventral and right dorsal regions. Therefore, we used multiple regression to determine whether, across both age groups, age, anterior callosal FA, and confident item memory accounted for independent proportions of the variance in frontal subsequent memory effects in left ventral and right dorsal IFG regions. We constructed separate regression models with either left ventral or right dorsal frontal subsequent memory effects as the dependent variable and age, anterior callosal FA, and confident item memory performance as the predictor variables. In the left ventral IFG (peak: [-36 34 -11]), the regression model was significant ($F_{3,38}=4.14$, $p<.05$. $R^2=.246$), with confident item memory and anterior callosal FA (but not age) accounting for significant proportions of the variance ($p=.021$ and $.045$, respectively). In the right dorsal IFG (peak: [48 14 25]), the regression model was also significant ($F_{3,38}=4.72$, $p<.01$. $R^2=.272$), with confident item memory and anterior callosal FA (but not age) accounting for significant proportions of the variance ($p=.03$ and $.01$, respectively). When confident item memory was replaced with confident source accuracy as a predictor variable

in separate regression models, the same relationships were observed for both left ventral and right dorsal IFG regions, with confident source accuracy independently predicting frontal subsequent memory effects in left ventral IFG ($p=.02$) and, in a separate model, right dorsal IFG ($p=.04$).

Predictors of Memory Performance

We next used multiple regression to address whether, across both groups, the combination of age, anterior callosal FA, and either left ventral or right dorsal subsequent memory effects predicted confident item memory performance. The model was significant when subsequent memory effects in left ventral IFG were included as a predictor variable ($F_{3,38}=3.18$, $p=.035$, $R^2=.201$). However, only left ventral IFG effects accounted for a significant proportion of the variance ($p=.021$). A separate model with subsequent memory effects in right dorsal IFG replacing left ventral IFG effects was also significant ($F_{3,38}=2.89$, $p=.048$, $R^2=.186$), although only right dorsal IFG effects accounted for a significant proportion of the variance ($p=.031$).

Relationship between Hippocampal Effects and Negative Effects

The final analysis was motivated by the findings of Miller et al. (2008), where less hippocampal activation was associated with increased disengagement of medial parietal regions. Parameter estimates were extracted from a 3mm-radius sphere centered around the peak voxel (-27 -12 -23) in the left hippocampal region found to demonstrate age-invariant positive subsequent memory effects for source memory. We then computed the correlation

across subjects, controlling for age, between the magnitude of positive subsequent source memory effects in this hippocampal region with the mean magnitude of negative subsequent source memory effects across the 8 age-invariant regions identified in Chapter 2 (Section 2.3.3). Consistent with Miller et al. (2008), there was a significant negative relationship ($r = -.328, p < .05$) between positive hippocampal effects and negative effects, with less disengagement of regions associated with increased hippocampal activity. When a separate correlation was computed for the older group, the relationship was not significant.

3.4 DISCUSSION

The present chapter investigated the neural correlates of successful memory encoding for non-verbal items across younger and older subjects. Age-invariant positive subsequent item memory effects were evident in several cortical regions including bilateral inferior frontal gyrus. At a reduced statistical threshold, age-invariant subsequent source memory effects were identified in right fusiform gyrus and left hippocampus. Across both age groups, anterior FA was positively correlated with left and right frontal subsequent memory effects. In specific left (ventral) and right (dorsal) IFG regions, the magnitude of frontal subsequent memory effects was positively correlated with both confident item memory and confident source accuracy. We discuss the implications of these findings for the understanding of ‘right frontal over-recruitment’ and age-related episodic memory decline below.

3.4.1 DTI Data

The age-related reduction in anterior, but not posterior, FA observed in the present study is consistent with prior studies that have demonstrated greater age-related differences in white matter integrity in anterior compared to posterior regions (Head et al. 2004; Pfefferbaum et al. 2005; Madden et al. 2009; de Chaselaine et al. 2011). FA is a scalar measure of directional diffusion and is considered to be a putative measure of axonal diameter and myelination (Basser and Pierpaoli 1996; Beaulieu 2002). One explanation for the gradient in age-related reduction in callosal FA from posterior to anterior regions is the notion that brain regions that mature last during development are the first to decline (Raz et al. 2000). Another explanation for the anterior-posterior gradient in callosal FA reduction stems from the finding that anterior callosal regions contain a larger percentage of smaller diameter fibers which are less myelinated – and myelinated by fewer oligodendrocytes – in comparison to posterior regions. Thus, these anterior callosal regions are more susceptible to neural degradation (both due to smaller diameter fibers, as well as being differentially impacted by astrocyte death). The finding that, across all subjects (and in the older group alone), increased anterior callosal FA was predictive of faster RTs is consistent with prior reports of white matter integrity differences mediating decline in processing speed (Kennedy and Raz 2009; Salami et al. 2012). It is important to note, however, that mean study RT did not differ between age groups, despite the finding that older subjects demonstrated significantly lower anterior callosal FA measures. Thus, while processing speed (indexed, in this case, by study RTs) may be mediated by anterior callosal FA differences, it is not known this relationship is directly mediated by a callosally-specific mechanism. Rather, FA may

simply be a proxy for there are other mediating factors – such as general neural integrity – that contribute to differences in processing speed.

3.4.2 fMRI findings

Age-invariant subsequent memory effects

Consistent with prior studies using non-verbal stimuli, positive subsequent memory effects for item memory were found in bilateral IFG in both younger and older subjects (Gutchess et al. 2005; Mormino et al. 2012). In contrast to studies utilizing verbal materials (Morcom et al. 2003; Duverne et al. 2009), we found little evidence of over-recruitment of the right hemisphere in older subjects. Specifically, both a voxel-wise analysis and a region-of-interest approach demonstrated equivalent engagement of bilateral frontal regions in young and older adults. This finding suggests that recruitment of the right IFG in older subjects is not always indicative of age-related ‘over-recruitment’ (see Introduction, Section 1.5.2), as previous studies using verbal materials have suggested (Morcom et al. 2003; Duverne et al. 2009). The present findings suggest that, in circumstances where memory performance is high in both age groups and healthy young subjects demonstrate bilateral frontal subsequent memory effects, older subjects recruit bilateral IFG regions to the same degree – and not greater, or more extensively.

Age-invariant subsequent source memory effects - Hippocampal Subsequent Source Memory Effects

As noted in Chapter 1 (Section 1.5.1), prior studies of age-related differences in memory encoding have reported differences in MTL effects, with some studies demonstrating decreased responsivity of the MTL with age (Gutchess et al. 2005; Dennis et al. 2008) and other studies demonstrating age-invariant MTL effects (Morcom et al. 2003; Duverne et al. 2009; de Chastelaine et al. 2011). At a reduced threshold ($p < .01$), we identified an age-invariant positive subsequent memory effect specific for source memory in the left hippocampus. This finding (admittedly, at a reduced experimental threshold), along with prior findings of age-invariant hippocampal effects (Morcom et al. 2003; Duverne et al. 2009; de Chastelaine et al. 2011), suggests that there is not a generic diminution in the responsivity of the hippocampus with age (cf. Ramsøy et al. 2012). The discrepancy in prior reports may be explained by the degree to which the different experimental procedures specifically index recollection, control for memory strength, and ensure that older and younger subjects are matched (or near-matched) in memory performance.

The magnitude of positive subsequent source memory effects in the left hippocampus was negatively correlated with the age-invariant negative subsequent source effects reported in Chapter 2 (Section 2.3.3). This finding is consistent with the relationship reported previously by Miller et al. (2008), where lower-performing older subjects who demonstrated attenuated negative subsequent memory effects were found to demonstrate ‘compensatory’ increases in hippocampal activation. It is important to note, however, that in the present study, the negative relationship between positive hippocampal effects and negative subsequent source effects was observed in the context of age-*invariant* effects, suggesting

that the relationship between encoding-related activations and ‘deactivations’ is not specific to older individuals.

Relationship between frontal effects and callosal integrity

Across both age groups, controlling for age, we found a positive relationships between anterior callosal FA and the magnitude of left and right frontal subsequent memory effects. This finding is consistent with the positive correlation between right frontal activity and anterior callosal FA reported by de Chastelaine et al. (2011), and suggests that engagement of both left and right frontal PFC regions may be facilitated by higher callosal FA. However, as noted by de Chastelaine et al. (2011), it is not known whether differences in the magnitude of frontal subsequent memory effects mediated by callosal FA reflect possible changes in neural integrity versus efficiency of inter-hemispheric communication. Further studies are needed to more directly address this question.

It is important to note that prior studies investigating the relationship between DTI measures and fMRI activation have reported mixed results (see Bennett and Rypma 2013 for review). A prior study by Persson et al. (2006), for example, reported a negative relationship between right frontal activation and anterior FA in older subjects during a verbal encoding task. Another study by Putnam et al. (2008), using a verbal encoding task, reported a similar negative relationship between the recruitment of right frontal PFC and anterior FA. These relationships were both observed, however, for right frontal activity relative to baseline as opposed to successful versus unsuccessful memory encoding.

Relationship between frontal effects and memory performance

Consistent with de Chastelaine et al. (2011), left frontal subsequent memory effects (in ventral IFG) were positively associated with memory performance (as indexed by both confident item memory and confident source accuracy). However, whereas prior studies of memory encoding using verbal materials have reported a negative association between right frontal subsequent memory effects and memory performance (Duverne et al. 2009; de Chastelaine et al. 2011), the present study using *non-verbal* materials found a *positive* relationship between right frontal effects (in dorsal IFG) and memory performance (again, as measured both by confident item memory and confident source accuracy). The negative relationship between right frontal subsequent memory effects and memory performance observed in previous studies therefore appears to depend upon the employment of study items and tasks that elicit left-lateralized effects in young subjects.

de Chastelaine et al. (2011) proposed that the negative relationship between right frontal effects and memory performance did not necessarily mean that right frontal effects reflect general age-related changes that are detrimental to mnemonic function (Buckner and Logan 2002; Logan et al. 2002). Instead, the authors suggest that right frontal effects may reflect processes that partially compensated for decline in left PFC function. As such, recruitment of right frontal regions may help meet the on-line demands of the study task, but not contribute to successful memory encoding – which, in the case of verbal materials, is only supported by left frontal regions. The present findings are thus consistent with this partial compensation hypothesis, in that recruitment of right frontal regions during the

encoding of *non-verbal* items contributes to both online demands of the study task as well as successful memory encoding.

Multiple Regression Analyses

When anterior callosal FA and confident item memory performance were entered (across all subjects, controlling for age) as predictor variables into separate regression models with left and right frontal effects as dependent variables, anterior FA and confident item memory accounted for approximately 25% of the variance in left frontal subsequent memory effects and 27% of the variance in right frontal subsequent memory effects. Each of the predictor variables was independently significant in both models. These findings highlight the possibility that

3.4.3 Concluding comments

The present findings provide evidence that, in task-stimuli combinations which give rise to bilateral frontal subsequent memory effects in healthy young subjects, older subjects do not demonstrate greater (or more extensive) recruitment of right frontal IFG regions. Moreover, the present findings suggest that processes indexed by anterior callosal FA may mediate the engagement of frontal IFG regions in both left and right hemispheres. In contrast with prior verbal encoding studies where right frontal engagement was associated with poorer memory performance, the magnitude of right frontal effects in dorsal IFG regions was *positively* correlated with both item and source memory performance. This opposite relationship – as well as a demonstrated positive relationship between memory performance

and left frontal effects – supports the notion that bilateral processing of non-verbal items at study is beneficial to later memory encoding across both young and older subjects.

Figure 3.1. Mean FA values (\pm SE) from the anterior and posterior corpus callosum ROIs according to age group.

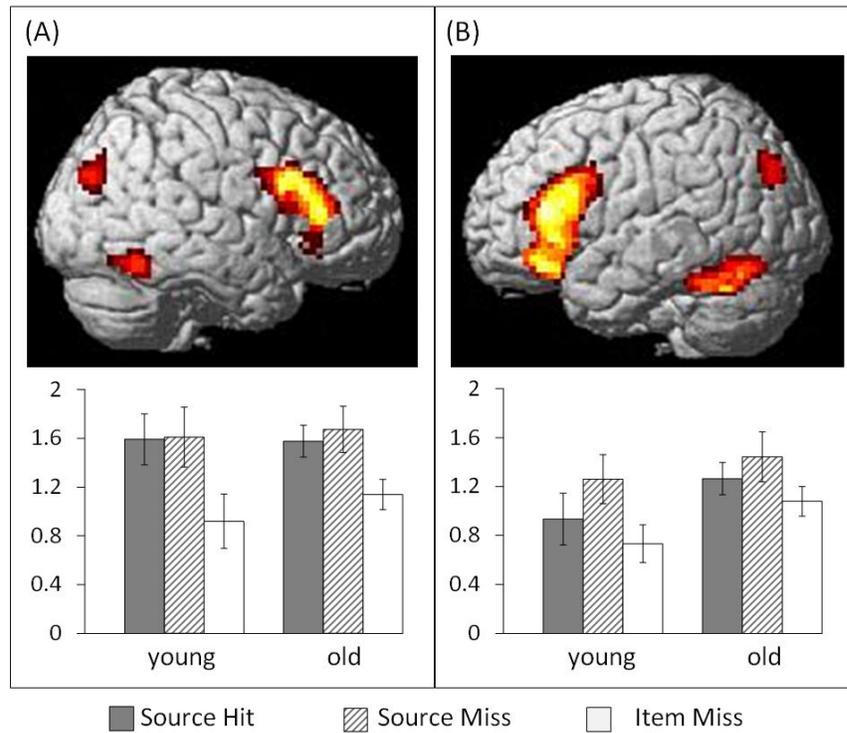


Figure 3.2. Regions demonstrating age-invariant positive subsequent item memory effects in left (A) and right (B) hemispheres. Bar charts depict mean across-region parameter estimates (arbitrary units) in left (A) and right (B) inferior frontal gyrus. ‘Source hit’ condition included for purely illustrative purposes.

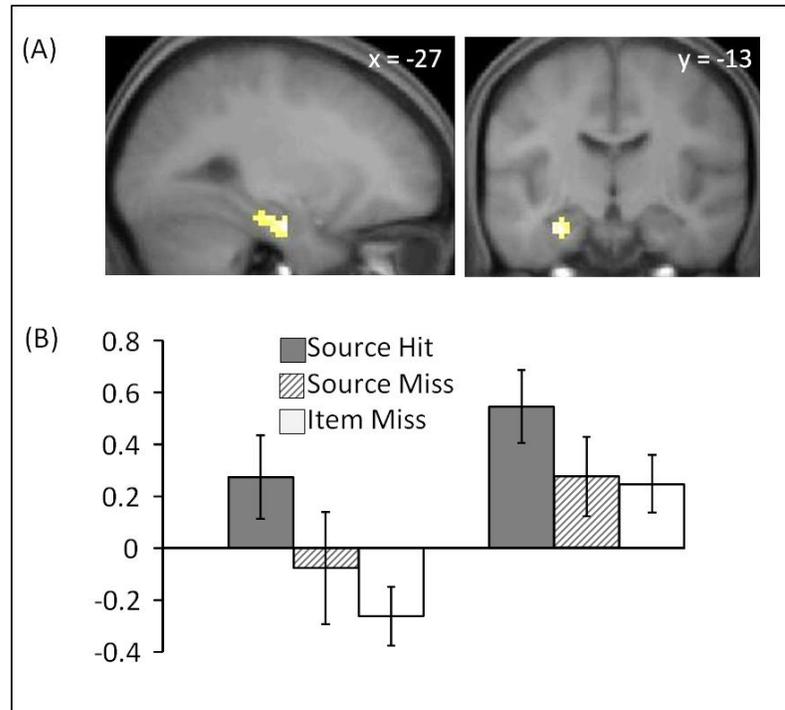


Figure 3.3. (A) Sections of left hippocampal region demonstrating subsequent source memory effects (item+context > item only) common to young and older subjects (reduced threshold of $p < .01$) superimposed onto sections of the normalized T1-weighted image averaged across all subjects. (B) Bar plot showing parameter estimates (in arbitrary units) and standard errors from peak voxel in left hippocampus (-27 -13 -23). ‘Item only’ condition included for illustrative purposes only.

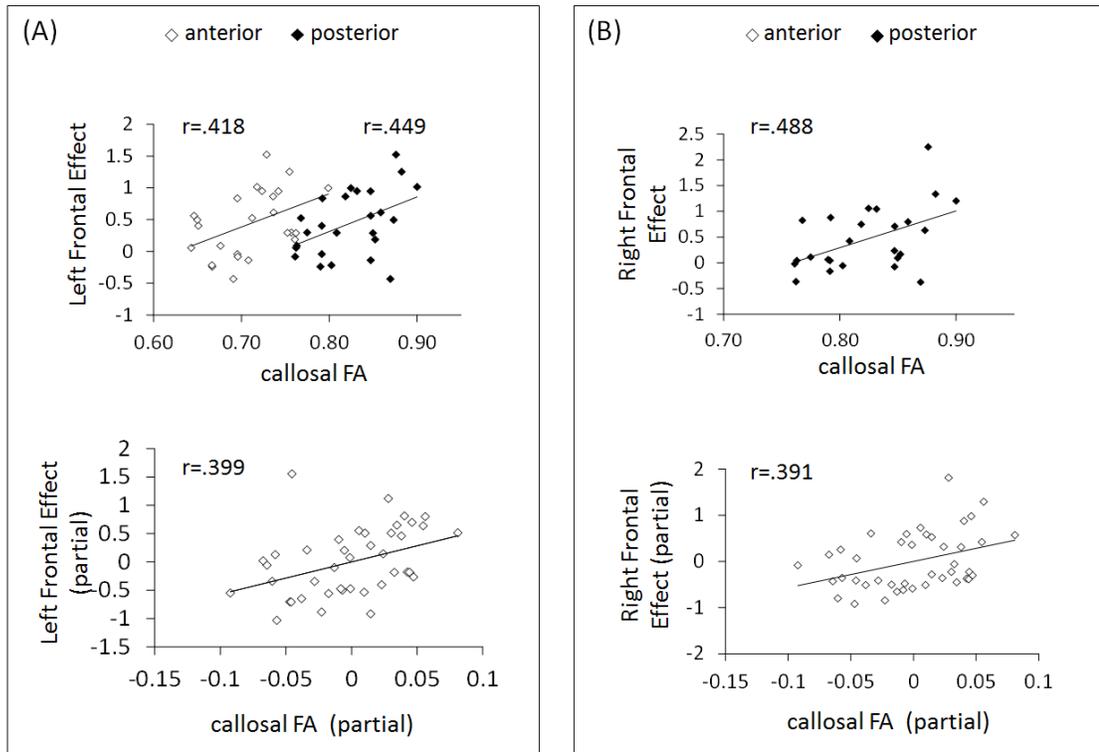


Figure 3.4 (A) Plots showing the relationship between left frontal overall subsequent memory effects and callosal FA in older subjects (top) and across all subjects, controlling for age (bottom). (B) Plots showing the relationship between right frontal overall subsequent memory effects and callosal FA in older subjects (top) and across all subjects, controlling for age (bottom).

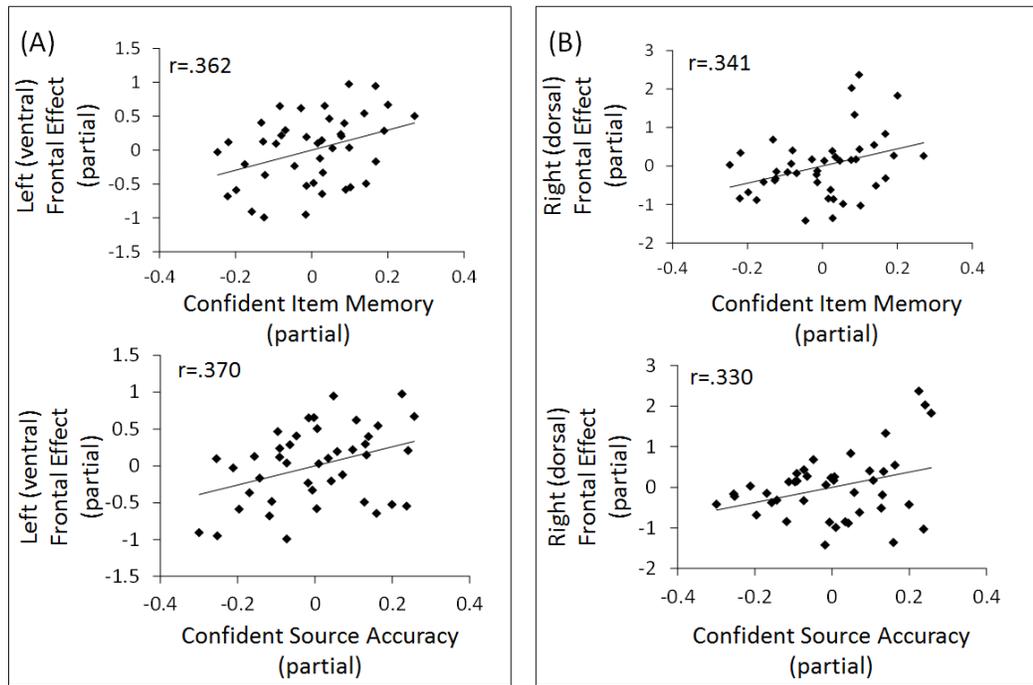


Figure 3.5 (A) Partial plots showing the relationship across all subjects (controlling for age) between left (ventral) frontal overall subsequent memory effects and confident item memory (top) and confident source accuracy (bottom). (B) Partial plots showing the relationship across all subjects (controlling for age) between right (dorsal) frontal overall subsequent memory effects and confident item memory (top) and confident source accuracy (bottom).

Table 3.1. Age-invariant positive subsequent item memory effects

Coordinates			Peak Z	Number of above- threshold voxels	Region
x	y	z			
-45	29	7	5.55	1005	L inferior frontal gyrus
-27	26	-2	4.79	1005 subpeak	L inferior frontal gyrus
-36	32	-11	4.76	1005 subpeak	L inferior frontal gyrus
-9	26	43	3.56	46	L superior medial gyrus
-39	-58	-20	5.24	288	L cerebellum
-27	-76	34	4.27	94	L middle occipital gyrus
36	29	-2	4.79	585	R inferior frontal gyrus
48	17	22	4.69	585 subpeak	R inferior frontal gyrus
54	29	16	4.31	585 subpeak	R inferior frontal gyrus
48	-58	-17	4.04	60	R inferior temporal gyrus
33	-79	28	4.02	83	R middle occipital gyrus

Table 3.2. Age-invariant positive subsequent source memory effects (reduced threshold: $p < .01$)

Coordinates			Peak Z	Number of above-threshold voxels	Region
x	y	z			
-27	-13	-23	3.00	42	L hippocampus
36	-34	-14	3.19	31	R fusiform gyrus

CHAPTER FOUR

EFFECTS OF CONTEXT-TYPE ON SUBSEQUENT MEMORY EFFECTS ASSOCIATED WITH THE ENCODING OF ITEM-CONTEXT MEMORIES

4.1 Introduction

The ability to successfully form associations between an item and its spatiotemporal context is a critical feature of episodic memory (Tulving 1983). As noted in Chapter 1 (Section 1.3), one way in which episodic memory is operationalized in the laboratory is by employing source memory tests where subjects are tested for their ability to recollect a specific contextual feature (or ‘source’) associated with a study item. One distinction that has been made in the source memory literature is between ‘external’ versus ‘internal’ source contexts (Johnson et al. 1993). ‘External’ contexts pertain to information that is present in the study environment, whereas ‘internal’ contexts refer to information that is generated by the subject during study and not present in the external study environment (Taylor & Henson 2012).

In fMRI studies of memory encoding, examples of ‘external’ contexts that have been commonly used include memory for color (Staresina et al. 2006; Staresina & Davachi 2008; Uncapher et al. 2006, 2009), location (Cansino et al. 2002; Park et al. 2008; Uncapher et al. 2006, 2009; Gottlieb et al. 2012), and sensory modality (Gottlieb et al. 2010, 2012; Park et al. 2012). A commonly used ‘internal’ source context is memory for the decisions made about an item at study (i.e. memory for encoding task; Davachi et al. 2002; Gold et al. 2006; Kensinger & Schacter 2006; Duarte et al. 2011). Two studies have employed a combination

of internal and external encoding contexts, such as having one of two colors signal one of two encoding tasks (Ranganath et al. 2004; Kirwan et al. 2008), making it difficult to determine whether effects are specific to one type of encoding context.

One prior study by Staresina and Davachi (2008) has compared memory for encoding task with an external source feature (color). These authors focused on findings within the medial temporal lobe and found that the hippocampus predicted memory for item-task and item-color associations, while the perirhinal cortex only predicted memory for item-color associations (Staresina and Davachi, 2008). It is unknown whether similar context-specific differences exist outside the MTL.

In addition to the heavy focus on the MTL in studies of source memory encoding (Davachi et al. 2002; Gold et al. 2006; Kirwan et al. 2008; Staresina & Davachi 2008; Duarte et al. 2011), fMRI studies using the subsequent memory procedure (Paller and Wagner 2002) to investigate source memory encoding have for the most part limited reported effects to ‘positive’ subsequent memory effects (greater activity for later remembered compared to later forgotten study items). Regions demonstrated ‘negative’ effects (later remembered < later forgotten) for item-context memory encoding remaining relatively under-reported. Studies that *have* reported negative item-context effects (Kirwan et al. 2008; Duarte et al. 2011; Gottlieb et al. 2012; Mattson et al. in press – see Chapter 3) have demonstrated negative subsequent memory effects in a number of cortical regions (see Tables 1.1 and 2.5 for reference). Specifically, Duarte et al. (2011) reported negative effects in a number of cortical regions including bilateral middle cingulate cortex, left precuneus, right posterior cingulate cortex for item-task memory. In contrast, Mattson et al. (in press – see Chapter

2.3.3) reported negative item-task effects in more anterior regions, including medial and bilateral insula/frontal operculum. Negative effects for item-location memory reported in Gottlieb et al. (2012) were limited to medial parietal cortex and occipital cortex.

The current study directly compared memory for two types of item-context associations and addressed the question of whether subsequent memory effects for item-task and item-location memory differ depending on the type of context (task versus location) being encoded. Subjects were scanned while making size or location ('task' context) judgments on pictures representing every-day objects that appeared on the left or right side of fixation ('location' context). Importantly, subjects made confidence judgments for item memory responses to control for strength of item memory when distinguishing between successful versus unsuccessful item-context memory encoding (discussed in Section 1.2; see Squire et al. 2007; Kirwan et al. 2008; Wais et al. 2010). Study items receiving a 'confident old' judgment were segregated according to whether they went on to be given correct source judgments for both task and location ('task+location'), correct judgment for task but not location ('task only'), correct judgment for location but not task ('location only'), or incorrect source judgments for both task and location ('item only'). Thus, the contrast between 'task+location'/'task only'/'location only' and 'item only' trials permitted identification of the neural correlates of item-context associations unconfounded by differences in item memory strength.

Prior studies of multi-featural encoding have demonstrated conjoint subsequent memory effects, that is, subsequent memory effects uniquely associated with the encoding of both contextual features, and not either feature alone (Uncapher et al. 2006; Gottlieb et al. 2012).

Positive conjoint effects for location and color have been previously reported in the right intraparietal sulcus (IPS; Uncapher et al. 2006) and positive conjoint effects for location and sensory modality have been reported in right lateral occipital cortex (LOC; Gottlieb et al. 2012). These findings are thought to possibly reflect the benefit to encoding that results from engaging regions involved in mediating attention shifts (such as the IPS) and perceptual processing of object structure (such as the right LOC). In contrast, negative conjoint effects have been previously reported in the bilateral temporo-parietal junction (Gottlieb et al. 2012). This finding is thought to reflect the benefit to encoding that results from attention being directed toward task-relevant information, and away from task-irrelevant events (Uncapher et al. 2006). It is not known whether conjoint effects exist for the encoding of task+location information.

4.2 Materials and Methods

4.2.1 Subjects

Thirty-two healthy young adults (12 females) aged between 18 and 29 years (mean age: 24 yrs) participated in the experiment. Young adults were recruited from the undergraduate and graduate student population of University of Texas at Dallas (UTD) and graduate student population of University of Texas Southwestern Medical Center. Subjects were screened for histories of neurological, cardiovascular, or psychiatric illness, and contraindications for MR imaging. None of the subjects enrolled in the study were taking CNS-active medication. All subjects had normal or corrected-to-normal vision, were right-

handed, and learned English as their first language or before age 5. All subjects gave informed consent prior to participating, and were remunerated for their participation in accordance with the human subjects procedures approved by the University of Texas Southwestern Medical Center and the University of Texas at Dallas. Data collected from 13 subjects were excluded because of insufficient trial numbers for fMRI events of interest.

4.2.2 Stimulus Materials

Three hundred ninety-four stimulus pictures were used in the experiment. The colored pictures depicting everyday objects were drawn from Hemera Photo Objects 50,000 Volume III. Of the 394 pictures, 10 served as buffers (two at the beginning and end of each study list, and two at the beginning of the test list) and 48 additional pictures were used as practice items before the study and test phases. Of the remaining 336 pictures, 224 were assigned to the ‘study’ condition while 112 were assigned as ‘new’ items.

Two study lists were created from the 224 study pictures for each subject. Each list contained a pseudo-randomized ordering of 112 pictures (56 ‘size’ and 56 ‘where’ judgments, with an equal probability of being presented to the left or right of fixation) and 38 null trials, with no more than three consecutive presentations of items belonging to the same encoding task or presented on the same side of fixation. Test items comprised the 224 pictures from the study trials and 112 new pictures and were pseudo-randomized such that there were no more than three consecutive presentations of items belonging to the same experimental condition. All experimental stimuli were displayed using the Cogent software package implemented in MATLAB (<http://www.vislab.ucl.ac.uk/cogent.php>).

4.2.3 Experimental tasks and procedures

The experimental procedure consisted of a study task which took place during scanning over two study blocks, followed by a self-paced recognition memory test on a computer outside the scanner 15-20 minutes after the end of the scanning session. Prior to the scanning session, each subject was administered a 2 minute practice study (24 pictures, 8 'null' events). A four-minute structural scan was conducted prior to the study phase. Additionally, a second 1-minute practice session was administered inside the scanner immediately prior to the study phase.

Study Phase

During the study phase, two blocks of pictures (stimuli described above in Section 4.2.2) were administered, separated by a 1-minute break. A study cue preceding each picture was displayed for 750 ms (Helvetica, 30 point font) on either the left or right of fixation corresponding to the location of the upcoming picture. The location of the cue also signaled the hand subjects were to respond with, and was independent of the encoding task subjects were cued to make: 'S?' for a size judgment (bigger or smaller than a shoebox) and 'W?' for a where judgment (indoors or outdoors). The study picture was then presented for 1500ms and replaced with a white fixation cross in the same font and size as the study cue for 1750 ms, which was switched to a red fixation cross for 500 ms signaling the end of the trial. The stimulus onset asynchrony of study trials was a minimum of 4500 ms in duration and distributed stochastically, modulated by the addition of 76 null trials (Josephs and Henson, 1999). Study task responses were made with the index and middle fingers of each hand via a

hand-held button. The assignment of each finger to the smaller/indoors or larger/outdoors response was counterbalanced across subjects. Subjects were told their memories for the pictures and corresponding task/location would be tested later. Study instructions emphasized the need to respond quickly without sacrificing accuracy

Test Phase

Subjects were removed from the scanner after completion of the study phase and given instructions about the test phase. The test requirement was to judge whether the item had been presented at study and, if so, to indicate (in randomized order) which encoding task had been associated with the picture at study as well as which side of the screen the picture appeared on at study.

The test pictures were presented in central vision. Instructions were to make an old/new judgment on a 5-point confident scale, the options for which appeared below the picture in white letters: 'Conf-Old', 'Unconf-Old', 'Do-not-know', 'Unconf-New', 'Conf-New'. If one of the categories 'Do-not-know'/'Unconf-New'/'Conf-New' was selected, the test advanced to the next item. If a 'Conf-Old' or 'Unconf-Old' response was made, the following two encoding context judgments, in random order were required: 'Conf-S', 'Unconf-S', 'Do-not-know', 'Unconf-W', or 'Conf-W' and 'Conf-L', 'Unconf-L', 'Do-not-know', 'Unconf-R', or 'Conf-R'.

At test, the middle/index finger of the left hand was assigned to 'Conf-Old'/'Unconf-Old' respectively and index/middle/ring finger of the right hand assigned to 'Do-not-

know’/‘Unconf-New’/‘Conf-New’ respectively. Size/where and left/right responses were also made with the middle/index finger of the left hand assigned to ‘Conf-S’/‘Unconf-S’ for the task judgment and ‘Conf-L’/‘Unconf-L’ for the location judgment. The index/middle/ring fingers of the right hand were assigned to ‘Do-not-know’/‘Unconf-W’/‘Conf-W’ and ‘Do-not-know’/‘Unconf-R’/‘Conf-New’ for task and location judgments, respectively. A short (36 item) practice test was administered immediately prior to the 336-item test phase, which was self-paced, presented as a single block, and lasted approximately 30 minutes.

4.2.4 MRI Data Acquisition

MRI data acquisition was similar to the fMRI experiment reported in Chapters 2 and 3 (see Section 2.2.4), except a 32 channel headcoil was used instead of a transmit/receive radio frequency head coil to acquire both T_1 -weighted anatomical images (FOV 256x224, matrix size 256x224, voxel size 1x1x1mm, 160 slices, sagittal acquisition) and T_2^* -weighted echo-planar images (SENSE factor of 1.5, TR 2 s, TE 30 ms, flip angle 70°, FOV 240x240, matrix size 80x79). Each EPI volume consisted of 33 slices, (3 mm thick with 1 mm interslice gap, acquired in ascending order) and was oriented parallel to the AC-PC line. Functional data were acquired during each of the two study blocks (355 volumes per block) and concatenated across sessions prior to model estimation.

4.2.5 MRI Data Analysis

Data were preprocessed using a similar procedure as the data reported in Chapters 2 and 3 (see Section 2.2.5), except images were smoothed with an 8 mm (instead of 10 mm) FWHM Gaussian kernel and not re-normalized to a sample specific template.

The design matrix of the GLM included seven covariates that modeled events defined by subjects' responses during the test phase. Five events of interest were identified for the fMRI analyses: (1) studied items correctly and confidently endorsed as old that were associated with correct context responses for both task and location ('task+location'); (2) items correctly and confidently endorsed as old followed by a correct response for task but not location ('task only'); (3) items correctly and confidently endorsed as old followed by a correct response for location but not task ('location only'); (4) items correctly and confidently endorsed as old followed by an incorrect or 'don't know' response for both task and location contexts response ('item only'); and (5) items that were incorrectly given a confident or unconfident 'new' response ('item miss'). A sixth category consisted of items recognized with low confidence or given a 'don't know' response. These trials were modeled separately and not included in the fMRI events of interest. The seventh category of trials comprised events of no interest, namely buffer trials and trials associated with omitted or multiple study responses. Movement-related regressors (three rigid-body translations and three rotations determined from the realignment stage) and session-specific constant terms were also entered into the design matrix. Neural activity elicited by each event type was modeled by delta functions that coincided with the onset of each picture. The resulting

BOLD response was modeled by convolving the neural functions with a canonical hemodynamic response function (HRF). Parameter estimates for each condition were estimated using the same method as described in Section 2.2.4 and carried forward to the second level of analysis.

To identify voxels that differentiated the five events of interest in an unbiased manner, the respective parameter estimates were subjected to a one-way within-subject ANOVA implemented in SPM8 with five response category conditions (task+location, task only, location only, item only, item miss) specified for each subject. Contrasts derived from the ANOVA model were thresholded at $p < .005$. Control of Type I error was effected by imposing a cluster-wise threshold of $p < .05$, corrected for multiple comparisons within a whole-brain mask. The threshold was set at 47 contiguous voxels on the basis of a Monte Carlo simulation implemented in the Alphasim routine of the AFNI analysis package (NIMH, Bethesda; <http://afni.nimh.nih.gov/afni>).

4.3 RESULTS

4.3.1 Behavioral Results

Study Phase

Reaction times (RTs) to study items included in the fMRI analysis are given in Table 1 segregated according to subsequent memory condition. To assess whether RT varied with later memory, analysis of variance (ANOVA) with factor of memory condition (task+location, task only, location only, item only, item miss) was performed. There was no

significant effect of subsequent memory condition ($F_{1,18}=1.761$, $p=.202$). Thus, differences in subsequent memory effects for task versus location contexts are unlikely to be a consequence of differences in study reaction times.

Test Phase

Table 2 shows item memory performance on the later memory test. Mean item hit rate was .68 (SD=.13) against a false alarm rate of .05 (SD=.06). Source memory performance is summarized in Table 3. An overall measure of source recollection (pSr) was estimated using an index derived from a single high-threshold model (Snodgrass and Corwin 1988; for example, see Gottlieb et al. 2010). To correct for the influence of guesses, source hit rates were adjusted according to the formula, $p(\text{corrected source hit}) = [p(\text{source hit}) - .5(1 - p(\text{source don't know}))] / [1 - .5(1 - p(\text{source don't know}))]$. The adjusted source hit rates were .47 (SD=.14) and .31 (SD=.17) for task and location memory, respectively. Task memory performance was significantly better than location memory performance ($t_{18}=4.75$, $p<.001$ two-tailed).

4.3.2 fMRI results

ANOVA Main Effect

We first searched for regions demonstrating subsequent memory effects by taking the ANOVA main effect of condition (which identifies, in an unbiased manner, any regions where some linear combination of levels differs from another linear combination of levels) thresholded at $p<.005$, two-sided (cluster extent threshold = 47 voxels). The resulting SPM

identified the nine significant clusters listed in Table 4, including bilateral precuneus, bilateral middle frontal gyrus, left inferior frontal gyrus, right superior temporal gyrus, and bilateral insula/frontal opercular regions. In order to characterize these effects, we extracted parameter estimates from the peak voxels of each of these 8 clusters (Table 4, excluding left cerebellum), as well as a right precuneus subpeak of the main 2020-voxel cluster. Parameter estimates were subjected to ANOVA, employing factors of region and subsequent memory (task+location, task only, location only, item only, item miss). The ANOVA gave rise to a significant main effect of region ($F_{3,7,66,9}=14.48$, $p<.001$) which interacted with subsequent memory ($F_{9,3,165,7}=6.54$, $p<.001$).

Follow-up analyses in each separate region revealed a general pattern of task only=item only= item miss>task+location>location only in most regions. Figure 2 illustrates the pattern of activity in each of the nine regions listed in Table 4. The notable exception to this general pattern of activity was in the left ventral inferior frontal gyrus region (peak: -36 35 -8), which demonstrated a general pattern of task+location=task only>location only=item only=item miss (Figure 1b). Specifically, six out of 9 regions (left precuneus, right precuneus, left middle frontal gyrus, right precentral gyrus, left dorsal inferior frontal gyrus, and right temporal pole) demonstrated significant location subsequent memory effects (location only < item only), but none of the regions except left ventral IFG (where the task only activity was greater than item only activity) demonstrated significant subsequent memory effects for task. Subsequent memory contrasts for each of the nine regions are summarized in Table 4.5.

Positive Subsequent Memory Effects

Given the relative paucity of regions demonstrating positive effects in the prior analysis, we next searched for regions demonstrating positive subsequent memory effects at a more liberal threshold by inclusively masking separate t-contrasts (thresholded at $p < .05$, one-sided) for task+location (task+location > item only), task (task only > item only), location (location only > item only), and item (item only > item miss) subsequent memory effects with the ANOVA main effect of condition (thresholded at $p < .001$, two-sided). The resulting SPM contrast was thresholded at 24 voxels. Positive subsequent memory effects for task+location and task memory were identified in left inferior frontal gyrus (Figure 4.3, Table 4.6), whereas no regions were found to demonstrate positive subsequent memory effects for location memory. Positive subsequent memory effects for item memory were identified in a 47-voxel region in left precuneus (Figure 1c, Table 4.6).

Negative Subsequent Memory Effects

The analyses described above were repeated to identify regions demonstrating negative subsequent memory effects for task+location, task, and location memory. Negative subsequent memory effects for task+location memory were identified in bilateral middle frontal gyrus and right posterior cingulate cortex (Figure 4.4a, Table 4.6). Whereas negative subsequent memory effects for task memory were limited to clusters in right middle cingulate cortex and right middle frontal gyrus (Figure 4.4b, Table 4.6), negative subsequent memory effects for location memory – consistent with the prior analysis from the ANOVA main effect – were identified in a number of regions, including left precuneus, bilateral middle frontal gyrus, left inferior frontal gyrus, left superior frontal gyrus, right precentral

gyrus, and right temporal pole (Figure 2c, Table 4.6). Negative subsequent memory effects for item memory were identified in a 34-voxel region in left middle frontal gyrus (Figure 4d, Table 4.6).

Conjoint subsequent memory effects

We used the procedure adopted by previous studies of multi-featural encoding (Uncapher et al. 2006; Gottlieb et al. 2012) to investigate whether any regions demonstrated subsequent memory effects for task+location that exceeded those of task and location. The task+location subsequent memory contrast was inclusively masked with the separate contrasts for task+location versus task only and task+location versus location only. No regions were found where positive or negative subsequent memory effects for task+location memory exceeded those of both task and location memory.

Association of subsequent memory effects with memory performance

We assessed whether there was a relationship between memory performance and subsequent memory effects in regions identified from the unbiased ANOVA main effect. Parameter estimates were extracted from 5mm radius spheres centered around the peak voxels for each of the regions listed in Table 4.4. The magnitude of subsequent memory effects for task+location (task+location versus item only), task (task only versus item only), and location (location only versus item only) memory were correlated with memory performance (item memory, task memory, and location memory) for each region listed in Table 4.5.

In two out of the six regions demonstrating significant negative subsequent memory effects for location memory – left middle frontal gyrus and left dorsal inferior frontal gyrus — the magnitude of negative location effects was positively correlated with item memory (but not location memory) performance ($r=.494$ and $.559$ for left MFG and left dorsal IFG, respectively; $ps<.05$). Thus, as illustrated in Figure 4.5, the greater the level of disengagement at encoding that occurred in these regions, the better was later item memory performance. No other regions demonstrating significant subsequent memory effects in Table 4.4 were found to exhibit significant correlations with item, task, or location memory performance.

4.4 Discussion

The present study investigated the differences in subsequent memory effects associated with the encoding of task versus location source contexts. Positive subsequent memory effects were limited to the left inferior frontal gyrus for task+location and task memory, and not found at all for location memory. Negative subsequent memory effects were restricted to clusters in the middle cingulate cortex and right middle frontal gyrus for task memory, but were identified more widely for task+location memory and location memory. Negative subsequent memory effects for location memory in left middle frontal and dorsal inferior frontal gyrus regions were also positively correlated with item memory performance. Below, we discuss the implications of these findings and their possible relationship to previous reports of item-context subsequent memory effects.

4.4.1 Behavioral findings

The finding that location memory performance was significantly lower than task memory performance is inconsistent with the previous findings reported by Staresina and Davachi (2008), where memory for task was significantly lower than memory for an external source feature (i.e. color). However, the encoding task employed by Staresina and Davachi (2008) required subjects to generate a mental image of the stimulus item in the color indicated by the background, thus promoting unitization of item and context (Section 1.4.1).

4.4.2 fMRI findings

Positive subsequent memory effects

The finding of positive subsequent memory effects for task+location and task memory in the left ventral inferior frontal gyrus is in line with prior studies of source memory encoding that have found positive effects in small clusters in the left IFG (Ranganath et al. 2004; Cansino et al. 2002; Staresina et al. 2006; Uncapher et al. 2006; Gottlieb et al. 2010; Duarte et al. 2011; see Table 1.1 for reference). It is of note that while positive effects in the left IFG have been widely reported for item memory encoding and encoding of item-item associations (e.g. Sperling et al. 2003; Jackson and Schacter 2004; Prince et al. 2005; Chua et al. 2007; Park and Rugg 2008; Blumenfeld et al. 2011; see Kim 2011 for review), many studies of source memory encoding – including results of the prior study reported in Chapter 3 – have failed to identify subsequent memory effects in the IFG associated with the successful encoding of item-context memories (see Table 1.1 for reference; Kirwan et al. 2008; Park et al. 2008; Uncapher and Rugg 2009; Gottlieb et al. 2012).

One explanation for the general finding of limited IFG effects for source memory encoding compared to item (and item-item) memory encoding stems from explanation of the role of the IFG in semantic processing, as well as in selection of competing representations (Thompson-Schill 2003; Zhang et al. 2004; Grindrod et al. 2008). Specifically, IFG activation has been found to be associated with competing responses and selection among internal representations (Rowe et al. 2000; Thompson-Schill et al. 2005; Badre and Wagner 2007). It is possible that, compared to the location context, successful encoding of task information (with or without accompanying location information) required higher selection demands, such as an increased number of potential responses to choose from when making a task response. Location information, in contrast, was inherent to the stimulus item and did not require selection among competing semantic representations – except to respond with the appropriate hand (left versus right) at study.

It is noteworthy that, in contrast with the findings reported in Chapter 3 (Section 3.2.2), the present study did not find any regions within the ANOVA main effect where neural activity associated with the ‘item only’ condition differed significantly from the ‘item miss’ condition. The ‘item only’ condition in the present study, however, differed slightly from that reported previously in Chapter 3 in that only task information was tested for in the previous chapter. In other words, the ‘item only’ condition in the previous experiment may have contained information about additional (non-criterial) contextual features associated with the stimulus item, thus giving rise to positive effects in a number of cortical regions including bilateral inferior frontal gyrus and bilateral middle occipital gyrus (see Table 3.1) when compared to the ‘item miss’ condition’.

Additionally, at a relaxed experimental threshold, positive item effects were observed in left precuneus while negative item memory effects were observed in left middle frontal gyrus (Table 4.6). These item effects are markedly unconventional and directly opposite as those previously reported in Chapters 2 and 3, where positive item effects were observed in large regions within the left PFC (Table 3.1) and negative item effects were reported in left precuneus (Table 2.5). This peculiar ‘reversal’ of regions demonstrating positive and negative item effects is possibly explained by subjects adopting a more conservative response criteria as a consequence of having to make a 3-part response for each test item, leading to potentially higher levels of (albeit weak) criterial (and non-criterial) recollection associated with ‘item miss’ trials compared to in the prior study.

In other words, because subjects were tested for item memory, task memory, and location memory in three consecutive steps, they may have made an effort to limit ‘confident old’ item responses to items for which both task and location contexts were likely to be remembered. This change in response criteria is evidenced by the finding that the proportion of ‘confident old’ responses to old items were significantly lower in the present study compared to the previous study (means of .64 and .76, respectively; $t_{17,19}=4.06$, $p<.001$; see Tables 4.2 and 2.3) despite no significant differences in ‘confident old’ responses to new items (confident false alarms; $t_{17,19}=-1.56$, $p=.11$). It is therefore conceivable that the ‘item miss’ condition in the present study may have been associated with weak recollection – and, moreover, reflect greater strength of recollection compared to the ‘item only’ condition, where memory for task/location contexts were guaranteed to be absent. The contrast

between item miss and item only would thus reflect weak and weaker memories, producing item effects in the opposite direction as that observed previously.

The finding of limited positive item effects – as operationalized by item only > item miss – in the present study is consistent with the prior multi-feature encoding study of Uncapher et al. (2006), where positive subsequent memory effects were limited to small (10-16 voxel) clusters in left dorsal IFG, left perirhinal cortex, and bilateral posterior occipital cortex.

Negative subsequent memory effects

The present results demonstrate negative subsequent memory effects for location memory in a number of cortical regions including bilateral precuneus, left middle frontal gyrus, right precentral gyrus, right insula/frontal operculum, and left inferior frontal gyrus (Table 4.5). These findings are in marked contrast with the negative subsequent memory effects for task memory, which were not identified in any of the peak voxels of clusters demonstrating a main effect of subsequent memory (Table 4.4). As described earlier in Section 1.4.3, regions demonstrating negative subsequent memory effects have typically been found to overlap with the default mode network, a network of regions that demonstrates greater activity at rest compared to goal-directed behavior (see Buckner et al. 2008 for review). However, the present finding of negative item-context effects (in this case, for location memory as opposed to task memory) in frontal regions *outside* the default mode network such as left IFG and right insula is consistent with the findings reported in Chapter 2 (Section 2.3.3) for negative source effects.

One possible interpretation of the difference in negative effects for task versus location memory (i.e. negative effects in many regions for location memory but not for task memory) is that negative effects are depending on whether the context being encoded requires attention to the external study environment. By this account, because processing of the location context required more ‘external’ attention to the study environment compared to processing of the task context, encoding of location information required more disengagement of DMN regions compared to encoding of task information. This interpretation is limited by the fact that subjects were asked to respond with their corresponding left or right hand depending on the spatial location of the picture – a manipulation that arguably requires attention to ‘internal’ processes. Additionally, subjects were cued with an external cue (‘S?’ versus ‘W?’ appearing on the screen at study) to signal which encoding judgment they were expected to make, thus adding an ‘external’ component to the task context.

An alternative explanation for the general absence of negative task effects in comparison to the prior findings of negative task effects reported in Chapter 2 (Section 2.3.3, Table 2.5) stems from the explanation of negative effects in older subjects discussed in Section 2.4.2. In this proposal, negative subsequent memory effects in older subjects were absent in prior studies of item-item associative memory because efforts were not made to control for high strength of recollection. While the present study restricted source memory analyses to items that received a confident and correct old judgment, source correct trials were collapsed across confidence (due to insufficient trial numbers). This is in contrast with the previous study (Chapters 2 and 3) where source correct trials consisted of encoding trials

given a subsequent confident and correct judgment for both item *and* source memory.

Additionally, task pSr was significantly lower in the present study compared to the previous study (.65 and .47 respectively, $t_{34}=4.06$, $p<.001$). Thus, it is conceivable that negative task effects were absent in the present study (in contrast to the prior stud) due to weaker recollection strength.

By this account, the presence of negative location effects despite significantly lower location memory performance than task memory performance suggests that trials associated correct task judgments may have been solved by recollect as well as familiarity. For example, subjects may have more easily been able to recapitulate the ‘size’ versus ‘where’ encoding contexts at test and make correct task responses based on weak recollection or familiarity compared to the location context. This is consistent with the notion that mental reinstatement of the encoding context (Smith 1979) may benefit memory performance. Specifically, reinstating the mental operations that were engaged at study may have helped subjects identify which encoding task was performed at study, but not provided cues that assisted in the identification of perceptually derived information, such as the item’s location context (Roediger & McDermott 1995; Mitchell and Johnson 2009).

Association with memory performance

The findings of a positive correlation between negative location effects and item memory performance in left IFG and MFG regions are inconsistent with prior findings in Chapter 2 (Section 2.3.2, Figure 2.4a) which failed to demonstrate a significant relationship between negative effects and item memory performance. It is unclear why negative location

effects would correlate positively with item memory performance, especially given that there was no significant relationship between location memory performance and item memory performance in the present study ($r_{19}=.303$, $p=.207$).

It is important to note that negative subsequent memory effects reported in the present study – including effects in putative default mode regions such as the precuneus – were associated with marked above-baseline parameter estimates (see Figure 1.2) as opposed to below-baseline levels of activity. It is possible that these above-baseline parameter estimates were driven by inadequate time between stimuli presentation for the neural response to return to baseline. The added requirement of subjects to attend to the location of a preceding cue and prepare their appropriate hand for the encoding task response may have contributed to the ‘task-positive’ effects consistently observed in the present study (see Stark and Squire 2001 for discussion of baseline conditions in fMRI).

4.4.3 Concluding comments

The present study investigated the differences in subsequent memory effects associated with the encoding of task information versus the encoding of location information. The findings suggest that the encoding of location information is associated with greater disengagement of regions within and outside the default mode network compared to the encoding of task information. Importantly, unlike the encoding of location information, the encoding of task information appears to be supported by processes that are independent of negative subsequent memory effects. However, this dissociation may reflect the greater

capability of task memory to be supported by weak recollection, and may thus be limited to experimental circumstances where task memory strength is not tightly controlled

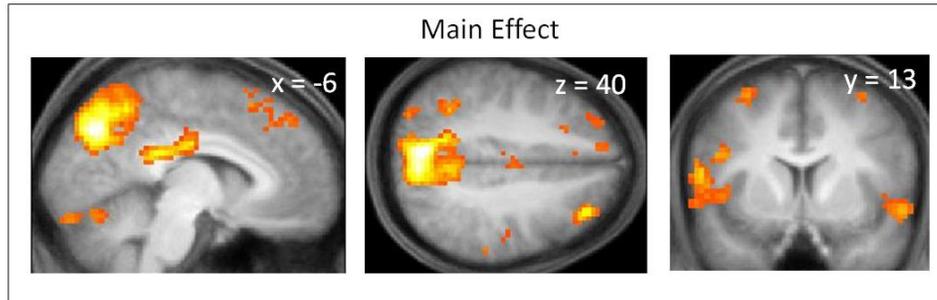
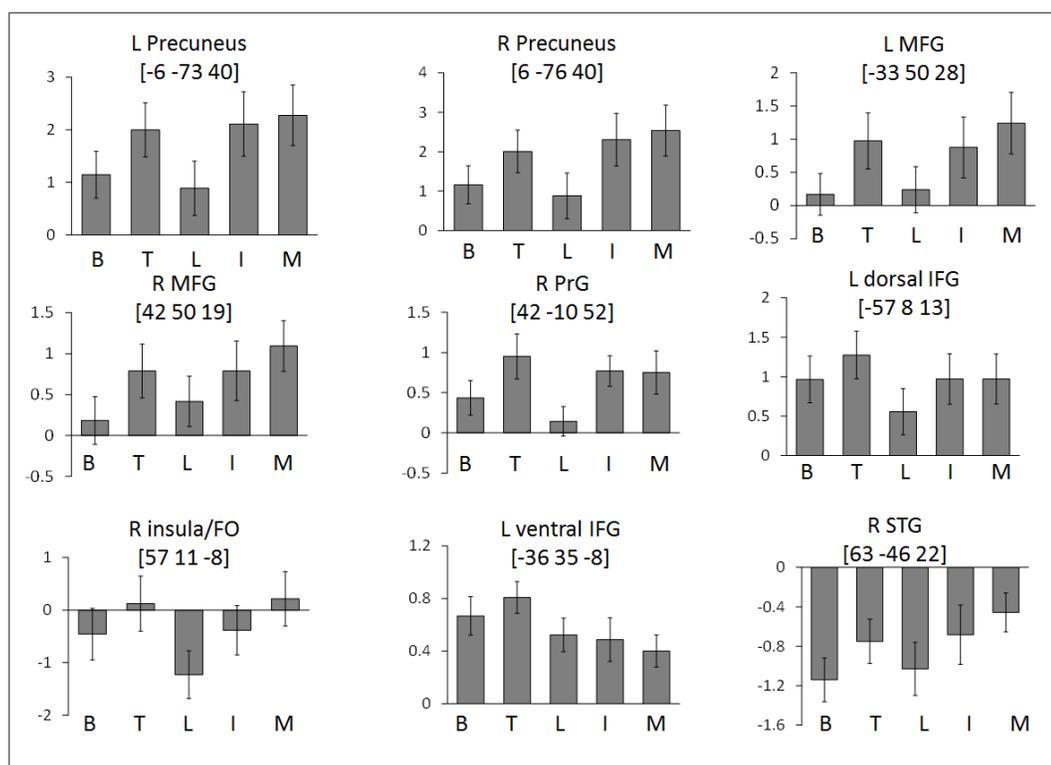
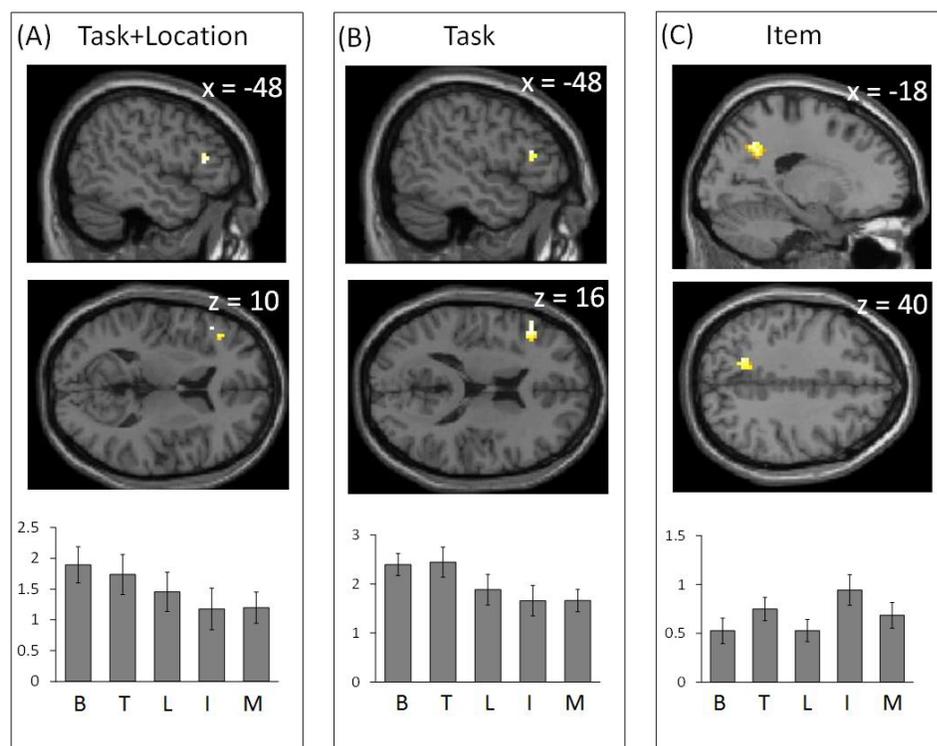


Figure 4.1 Subsequent memory effects identified from the ANOVA main effect.



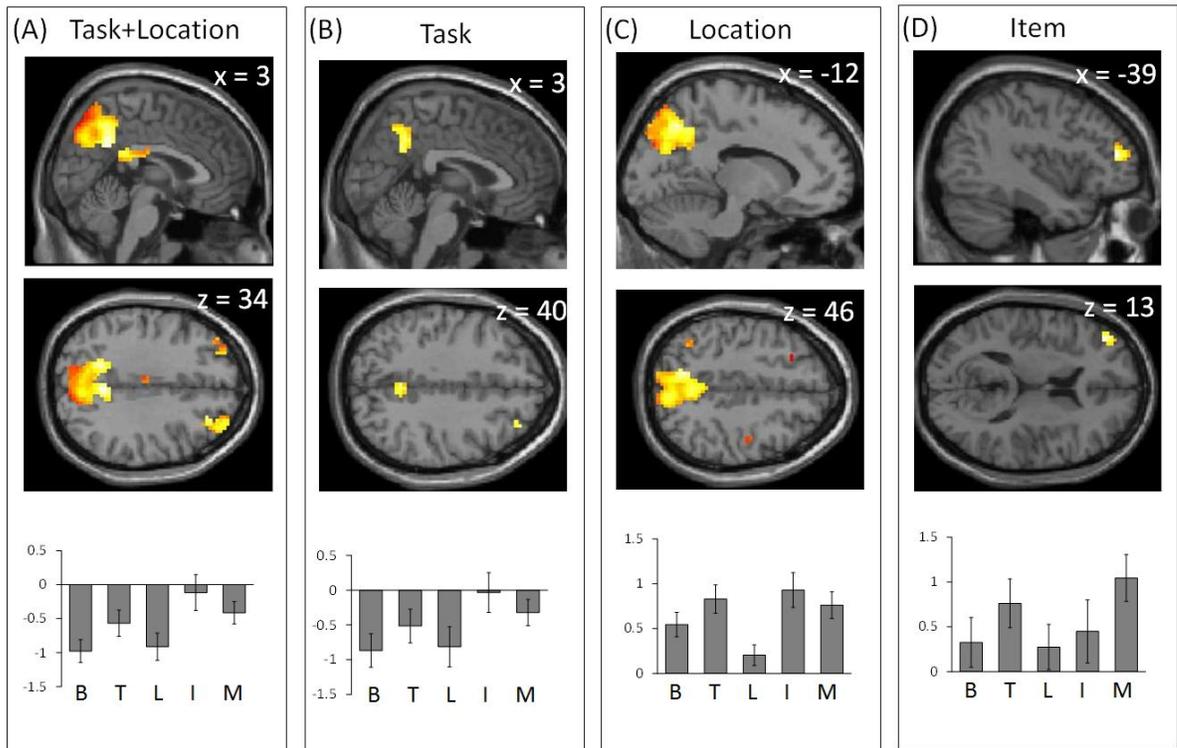
B= both (task+location); T= task only; L= location only; I= item only, M= item miss
MFG=middle frontal gyrus; IFG=inferior frontal gyrus; PrG=precentral gyrus; STG=superior temporal gyrus

Figure 4.2 Parameter estimates for the different subsequent memory conditions for each of the 9 peak regions identified from the ANOVA main effect.



B= both (task+location); T= task only; L= location only; I= item only, M= item miss

Figure 4.3 Positive subsequent memory effects for task+location (A), task (B), and item memory (C).



B= both (task+location); T= task only; L= location only; I= item only, M= item miss

Figure 4.4 Negative subsequent memory effects for task+location (A), task (B), and location memory (C).

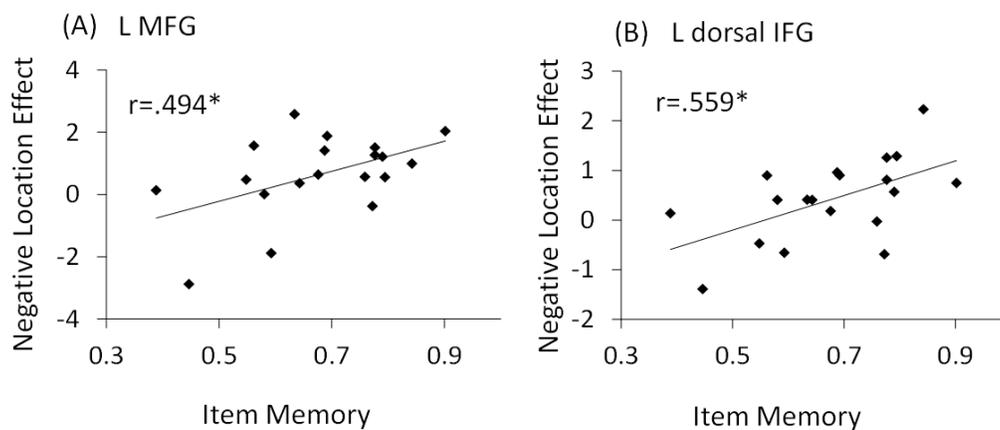


Figure 4.5 Scatterplots depicting relationship between negative subsequent memory effects for location memory and item memory performance in left middle frontal gyrus (A) and left dorsal inferior frontal gyrus (B). * $p < .05$

Table 4.1

Mean reaction times (ms) for trials used in fMRI analysis segregated by subsequent memory condition (\pm SD)

Task+Location	Task Only	Location Only	Item Only	Item Miss
1384 (286)	1368 (287)	1336 (310)	1348 (316)	1380 (292)

Table 4.2

Mean proportions of item memory judgments for old and new trials by response type (\pm SD)

	CO	UO	DK	UN	CN
Old	.64 (.14)	.09 (.09)	.05 (.04)	.07 (.07)	.15 (.15)
New	.03 (.04)	.03 (.04)	.04 (.05)	.22 (.23)	.69 (.26)

Note: Response abbreviations correspond to the following: CO, confident old; UO, unconfident old; DK, don't know; UN, unconfident new; CN, confident new.

Table 4.3

Mean proportions of source judgments for confidently and unconfidently recognized study items (\pm SD)

		Confident Source Correct	Unconfident Source Correct	Don't Know Source	Unconfident Source Incorrect	Confident Source Incorrect
Task	Confident Old	.57 (.11)	.17 (.10)	.06 (.05)	.08 (.04)	.12 (.10)
	Unconfident Old	.15 (.17)	.47 (.20)	.20 (.20)	.12 (.12)	.06 (.10)
Location	Confident Old	.32 (.15)	.32 (.13)	.09 (.08)	.17 (.11)	.09 (.12)
	Unconfident Old	.02 (.06)	.34 (.24)	.35 (.30)	.25 (.17)	.04 (.08)

Table 4.4. Main effect of subsequent memory condition

Coordinates			Peak Z	Number of above- threshold voxels	Region
x	y	z			
-33	50	28	4.91	778	L middle frontal gyrus
-36	35	-8	3.38	57	L inferior frontal gyrus
-57	8	13	3.78	142	L inferior frontal gyrus
-30	-43	-20	3.98	407	L cerebellum
-6	-73	40	5.04	2020	L precuneus
42	50	19	4.78	430	R middle frontal gyrus
57	11	-8	3.61	83	R temporal pole
42	-10	52	4.20	203	R precentral gyrus
63	-46	22	3.23	76	R superior temporal gyrus
6	-76	52	4.86	2020 subpeak	R precuneus

Table 4.5. Significant effects for regions demonstrating main effect of subsequent memory condition

	B vs T	B vs L	B vs I	B vs M	T vs L	T vs I	T vs M	L vs I	L vs M	I vs M
L precuneus	** ↓	ns	** ↓	*** ↓	*** ↑	ns	ns	*** ↓	*** ↓	ns
R precuneus	* ↓	ns	** ↓	*** ↓	*** ↑	ns	ns	*** ↓	*** ↓	ns
L MFG	*** ↓	ns	* ↓	*** ↓	*** ↑	ns	ns	* ↓	** ↓	ns
R MFG	*** ↓	ns	* ↓	*** ↓	* ↑	ns	ns	p=.059	*** ↓	ns
R PrG	* ↓	* ↑	ns	* ↓	** ↑	ns	ns	** ↓	** ↓	.ns
L dorsal IFG	* ↓	** ↑	ns	ns	*** ↑	ns	ns	* ↓	* ↓	ns
R insula/FO	* ↓	* ↑	ns	* ↓	** ↑	ns	ns	* ↓	** ↓	ns
L ventral IFG	ns	ns	ns	* ↑	** ↑	* ↑	** ↑	ns	ns	ns
R STG	* ↓	ns	* ↓	***	ns	ns	*	ns	** ↓	ns

*p<.05, **p<.005, ***p<.001, ns=not significant

B= both (task+location); T= task only; L= location only; I= item only, M= item miss

MFG=middle frontal gyrus; IFG=inferior frontal gyrus; PrG=precentral gyrus; FO=frontal operculum; STG=superior temporal gyrus; ↑= greater than; ↓=less than

Table 4.6
Positive and Negative Subsequent Memory Effects

	Coordinates			Peak Z	Number of above- threshold voxels	Region
	x	y	z			
Positive Effects						
Task+Location	-48	26	10	2.92	28	L inferior frontal gyrus
Task	-48	26	16	2.75	25	L inferior frontal gyrus
Item	-18	-58	-40	2.90	57	L precuneus
	-30	-55	-20	2.75	43	L cerebellum
Negative Effects						
Task+Location	-27	47	37	3.25	130	L middle frontal gyrus
	27	35	31	4.10	235	R middle frontal gyrus
	3	-55	34	4.27	995	R posterior cingulate cortex
Task	27	35	31	2.57	40	R middle frontal gyrus
	3	-52	40	2.30	88	R middle cingulate cortex
Location	-24	47	37	3.74	116	L middle frontal gyrus
	-21	32	52	2.20	23	L superior frontal gyrus
	-57	23	28	3.97	41	L inferior gyrus
	-33	-55	34	3.19	55	L intraparietal cortex
	-24	-58	-20	4.03	27	L cerebellum
	-12	-64	46	4.98	1045	L precuneus
	33	38	37	4.35	194	R middle frontal gyrus
	57	5	-8	2.65	29	R insula/frontal operculum
	9	-88	-17	3.46	25	R cerebellum
	42	-10	52	3.26	34	R precentral gyrus
12	-61	46	4.98	1045 subpeak	R precuneus	
Item	-39	44	13	2.88	34	L middle frontal gyrus

CHAPTER FIVE

SUMMARY AND DISCUSSION

5.1 Summary of Results

The advent of functional neuroimaging techniques (including fMRI) have enabled researchers to investigate the neural activity associated with the different stages of episodic memory. The study findings reported in the preceding chapters pertain to the first stage of memory – memory encoding – and utilized the subsequent memory procedure (Paller and Wagner 2002) to investigate brain regions demonstrating differences in neural activity at encoding predictive of later memory, as well as how these neural effects change in the context of healthy aging.

The preceding chapters discussed the effects of age on negative subsequent memory effects associated with the encoding of item and item-context information (Chapter 2), as well as the effects of age on positive subsequent memory effects associated with the encoding of non-verbal items (Chapter 3). Chapter 4 investigated whether subsequent memory effects differed depending on whether the encoding context was internally generated or an external feature of the stimulus item. Below, we summarize the findings of each chapter and discuss the significance of these findings. We also discuss limitations in the interpretations of these findings, as well as how these findings motivate future research.

5.1.1 Chapter 2: Effects of age on negative subsequent memory effects associated with the encoding of item and item-context information

In the fMRI experiment reported in Chapter 2 (and in Chapter 3), younger and older subjects were administered a series of pictures and asked to make one of two encoding judgments (size judgment versus indoor/outdoor judgment). Memory for pictures as well as the encoding task performed at study (source) was tested outside the scanner in a later recognition memory test. Importantly, confident ratings were incorporated and only items confident and correctly recognized at test were used in fMRI analyses in order to ensure that source memory effects were not confounded with item memory strength. The findings of this chapter focused on negative subsequent memory effects, or greater activity for later forgotten compared to later remembered items. As discussed previously (see Sections 1.4.3 and 1.5.3), negative subsequent memory effects have been found to overlap with the default mode network and are thought to reflect the benefit to encoding that results from re-allocating processing resources away from inwardly-directed events and toward external features. Regions of this network are of particular interest to the study of age-related cognitive decline, since they have been shown to be disrupted with normal age (Andrews-Hanna et al. 2007; Voss et al. 2010; see Mevel et al. 2011 for review). Additionally, prior studies have demonstrated reduced DMN activity in healthy older adults at rest (Damoiseaux et al. 2008; Koch et al. 2010) as well as reduced modulations of default mode activity during the processing of visual stimuli (Lustig et al. 2003; Gould et al. 2006).

Prior studies of memory encoding in younger and older subjects have demonstrated age-related reductions in negative subsequent memory effects associated with the encoding of items (Morcom et al. 2003, Gutchess et al. 2005; Duverne et al. 2009; Mormino et al. 2012) as well as item-item associations (Miller et al. 2008; de Chastelaine et al. 2011). The

findings reported in Chapter 2 suggest that, while this is the case for negative item effects, negative item-*context* effects do not demonstrate a reduction with age. Thus, age-related attenuation of negative effects reported previously are not likely the result of a more general failure on the part of older adults to disengage DMN regions in response to a stimulus event to the same extent as young adults (e.g. Lustig et al. 2003; Grady et al. 2006; Sambataro et al. 2010).

The difference in negative item effects in younger and older subjects can be attributed to the possibility that negative subsequent memory effects reflect encoding operations that benefit recollection, but do not affect familiarity. By this account, source miss trials may have been associated with greater levels of non-criterial recollection (Yonelinas and Jacoby 1994) in young subjects compared to older subjects, who relied more heavily on familiarity when making correct item judgments. This is consistent with the finding that older subjects show impairments in non-criterial recollection compared to young subjects (Toth and Parks 2006). Alternatively, differences in negative item effects between younger and older subjects may reflect the notion that familiarity is supported by multiple memory signals, which are differentially susceptible to advanced age (Duarte et al. 2008; Wang et al. 2012). Thus, it is possible that source miss trials may have been supported by familiarity-driven recognition in both groups, but that the familiarity signal was dependent upon encoding processes reflected in negative item effects for young, but not older subjects.

As illustrated in Figure 2.4, a positive correlation across both age groups was observed between the magnitude of age-invariant negative subsequent source memory effects – in DMN regions as well as frontal regions – and source memory performance. This is

consistent with prior studies that report a positive relationship in older subjects between negative subsequent memory effects and memory performance (Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2011; Mormino et al. 2012). Thus, the present findings suggest that the relationship between memory performance and negative subsequent memory effects does not vary with age.

5.1.2 Chapter 3: Effects of age on positive subsequent memory effects associated with the encoding of non-verbal items

The findings reported in Chapter 3 are from the same fMRI experiment as reported in Chapter 2, but focus on regions demonstrating positive subsequent memory effects (greater activity for later remembered compared to later forgotten items). The reported finding address the question of whether age-related ‘over-recruitment’ (see Section 1.5.2) of right frontal regions during encoding of verbal items – which elicit left-lateralized subsequent memory effects in young subjects – extends to the encoding of non-verbal items, which elicit more bilateral patterns of encoding-related activity (Gutchess et al. 2005; Sergerie et al. 2005; Garoff et al. 2005; Dickerson et al. 2007; Qin et al. 2007; Mormino et al. 2012). Consistent with prior studies of memory encoding using pictorial items (Gutchess et al. 2005; Mormino et al. 2012), positive subsequent memory effects were observed in bilateral inferior frontal gyrus (IFG) regions in both age groups, and no regions were found to demonstrate age-related differences in positive subsequent memory effects.

The finding of age-invariant subsequent source memory effects in the left hippocampus (albeit at a reduced statistical threshold) is in line with prior findings of age-

invariant positive subsequent memory effects in hippocampal regions (Morcom et al. 2003; Duverne et al. 2009; de Chastelaine et al. 2011). Together, these findings suggest that there is not a generic diminution in the responsivity of the hippocampus with age (cf. Ramsøy et al. 2012). Additionally, the negative relationship across both age groups between positive hippocampal age-invariant effects and negative age-invariant source effects reported previously in Chapter 2 extends previous findings of a similar relationship in older subjects (Miller et al. 2008). The findings of the present study suggest that relationship between encoding-related activations and ‘deactivations’ is not specific to older individuals.

The results reported in this chapter demonstrate a positive relationship between left frontal subsequent memory effects and memory performance, consistent with the findings of de Chastelaine et al. (2011). However, whereas prior studies of non-verbal memory encoding have demonstrated a relationship between right frontal subsequent memory effects and *poorer* memory performance in older subjects (Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2011), the results of this study demonstrated a *positive* relationship between right frontal effects and memory performance. Thus, the present findings suggest that right frontal subsequent memory effects do not necessarily reflect general age-related changes that are detrimental to mnemonic function (Buckner and Logan 2002; Logan et al. 2002). Instead, the findings support the notion that bilateral processing of non-verbal items at study is beneficial to later memory encoding across younger and older subjects. This is consistent with the ‘partial compensation hypothesis’ proposed by de Chastelaine et al. (2011) where, instead of reflecting processes that are inherently detrimental to encoding, right frontal effects reflect the engagement of processes that partially compensate for the

decline in left PFC function. Specifically, these processes may help to meet online demands of the study task but not benefit *verbal* memory encoding, which is supported by left-lateralized processes.

The findings of Chapter 3 also demonstrate a positive relationship between anterior callosal FA and the magnitude of left and right frontal effects across both younger and older subjects. This is consistent with prior findings of de Chastelaine et al. (2011), where anterior FA was found to be positively correlated with right frontal subsequent memory effects in older subjects. The present results, however, suggest that recruitment of left *and* right hemispheres are facilitated by relatively higher callosal FA, and that this relationship is not limited to older individuals. Moreover, in anterior FA (which was significantly higher in the young compared to older group) was associated with mean study reaction times in younger and older subjects, despite study RTs not differing between age groups. This finding highlights the need for further studies in elucidating the functional significance of differences in callosal FA and determining whether relationships between callosal FA and neural as well as behavioral measures reflect differences in the efficiency of communication between left and right hemispheres or general changes in structural integrity.

5.1.3 Chapter 4: Effects of context-type on subsequent memory effects associated with the encoding of item-context memories

The study reported in Chapter 4 addressed the question of whether subsequent memory effects differ depending on the type of context being encoded. Similar to methods employed in the previous study reported in Chapters 2 and 3, subjects were presented with pictorial

items and asked to make one of two encoding judgments depending on a preceding cue. An additional ‘location’ feature was added, where stimulus items appeared either to the left or right of fixation independent of the encoding task. In order to facilitate attention toward the stimulus location, subjects were required to respond with their appropriate left or right hand when making responses during encoding. A recognition memory test was administered outside the scanner, where subjects were asked to make item, task context, and location context responses using confidence ratings.

The absence of negative task effects in this study is in contrast with findings reported in Chapter 2. In the discussion section (Section 2.4.2) of this prior chapter, the absence of negative effects in older subjects is thought to reflect the notion that negative effects reflect processes that support strong recollection. In the present study, source memory judgments were collapsed across confident and unconfident context memory due to insufficient trial numbers, giving rise to a ‘task only’ condition that may have been associated with relatively weaker recollection compared to that reported previously. Thus, the relative absence of negative task effects in the present study compared to that reported in Chapter 2 (Table 2.5) can be attributed to possible differences in recollection strength.

The findings of negative location effects in a greater number of regions compared to negative task effects despite higher memory performance for task compared to location memory suggests that, in contrast with the location context, memory for the task context may have been solved by familiarity as well as recollection. This is consistent with the notion that source memory tasks are not all process pure and do not always exclusively rely on recollection (Yonelinas 1999). Specifically, mental reinstatement of the encoding context

(Smith 1979) may have benefited task memory performance, but not location memory performance.

The presence (at a reduced statistical threshold) of negative item effects – as operationalized by item only < item miss – in left middle frontal gyrus and positive item effects (item only > item miss) in left precuneus is highly unusual and in marked opposition with findings reported previously. It is possible that subjects in the present study may have adjusted their response criteria and have been reluctant to respond ‘confident old’ unless both task and location features were likely to be recollected. Thus, ‘item miss’ trials may have been associated with relatively *higher* levels of recollection compared to ‘item only’ trials (where memory for task and location context were ruled out), giving rise to an opposite pattern of effects as that reported in Chapters 2 and 3.

5.2 General Discussion

The results summarized above provide evidence that the prior findings of age-related attenuation of negative item (and item-item) subsequent memory effects does not extend to the encoding of item-context memories. If efforts are made to control for item memory strength and ensure that correct source judgments are more likely to index strong recollection, younger and older subjects do not demonstrate any age-related differences in negative source effects. Moreover, the magnitude of negative source effects was positively correlated with source memory performance across both age groups. These findings suggest that there is not a general failure on the part of older adults to disengage default mode network regions in response to a stimulus item. One question for future research is whether

the relationship between negative source effects and source memory performance is limited to the particular context employed (in this case, size versus where encoding task). Encoding judgments that are more self-referential, for example, have been shown to produce negative subsequent memory effects in default mode network regions in young subjects, but reversed effects in older subjects the same regions (Gutchess et al. 2010). It is not known whether negative item-context effects which *differentially* engage default mode regions in younger and older subjects (i.e. are not age-invariant) are positively associated with source memory performance.

The present research demonstrates that the negative relationship between right frontal subsequent memory effects and performance observed for verbal memory encoding does not apply to encoding circumstances where stimulus items are processed bilaterally. This suggests that right frontal subsequent memory effects are not a consequence of general age-related changes in neural function that are deleterious. One question for future research is whether, in task-stimuli combinations which elicit right-lateralized effects in healthy young subjects – such as the encoding of unfamiliar faces (Kelley et al. 1998), engagement of left frontal regions is still associated better memory performance. The partial compensation hypothesis predicts that, in these circumstances, recruitment of left frontal regions may reflect processes that help meet the on-line demands of the encoding task, but not be associated with successful encoding.

Future experiments are required to elucidate the functional significance of the positive relationship observed between anterior callosal FA and the magnitude of left and right frontal effects. It is not known whether this relationship reflects differences in neuronal integrity or

efficiency of communication between left and right hemispheres. More accurate measures of fiber integrity such as differential diffusivity (Leow et al. 2009) are needed in order to more directly address this issue. The present findings nonetheless speak to the potential importance of incorporating structure measures into analyses of age-related differences in subsequent memory effects.

The present findings highlight the importance of controlling for differences in memory strength not only when comparing subsequent memory effects between younger and older subjects, but also when comparing subsequent memory effects associated with different encoding contexts. As the findings of Chapter 4 suggest, differences in the degree to which source memory tests for two different encoding contexts index recollection may result in large differences in regions demonstrate subsequent source memory effects. Additionally, the degree to which ‘item only’ and ‘item miss’ trials are supported by non-criterial recollection versus familiarity may influence differences in subsequent item memory effects.

5.2.1 Concluding Comments

The findings of the preceding chapters demonstrate that, in circumstances where older subjects are required to make item-context judgments based in strong recollection, negative subsequent source memory effects – unlike negative item effects – are not attenuated with age. Moreover, greater negative subsequent source memory effects are associated with higher source memory performance across both age groups, suggesting that these effects

reflect processes that are beneficial to episodic memory encoding across younger and older subjects. Additionally, the findings of the preceding chapters demonstrate that, in task-stimuli combinations which elicit bilateral frontal subsequent memory effects in young subjects, the engagement of right frontal regions in older subjects is positively – as opposed to negatively – associated with memory performance. This suggests that recruitment of right frontal regions may reflect processes that support both on-line task demands as well as successful encoding of non-verbal materials.

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