THE NEURAL CORRELATES OF ENCODING MEMORY ASSOCIATIONS

by

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A veridical memory for an episodic event contains multiple pieces of information, which include associations between different items in the environment, temporal information about when different items were experienced, and contextual information such as where the items were experienced. In a series of three experiments presented in this dissertation, the subsequent memory procedure was used to investigate the neural correlates of successfully encoding these various types of episodic memory associations. The overarching aim of these studies was to identify neural correlates that indexed encoding operations that led to later successful memory for item-item, item-context, and temporal order information. Although each type of memory association had been investigated on its own in previous studies, the three experiments in this dissertation were the first to investigate the neural correlates of encoding item-item and item-context/temporal order associations within a common study episode. The first two experiments employed fMRI techniques to directly contrast the encoding of item-item and temporal order/item-context associations, respectively. The third experiment employed EEG/ERP techniques to directly contrast the encoding of item-item and item-context associations. Collectively, the findings across the three experiments further our understanding of the neural correlates underlying the memory encoding of different aspects of an experience.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1

INTRODUCTION: BACKGROUND AND SIGNIFICANCE

1.1 Episodic memory encoding

1.1.1 Theoretical framework of episodic memory

In the body of work to be reviewed, our interest lies in the subcomponent of memory known as episodic memory, which is defined as memory for a unique event, tied to the time and place when the event was initially experienced. Episodic memory involves a number of neural and cognitive processes that are engaged in the encoding, storage, and retrieval of information about an experience. These processes are intimately linked; the successful retrieval of a memory is thought to depend upon the degree to which processes engaged during encoding of the memory are re-engaged upon presentation of a retrieval cue (Rugg et al., 2008).

An early theoretical framework (Craik and Lockhart, 1972; Morton, 1970) viewed memory as a byproduct of information processing. One of the main contributions of this "proceduralist" approach was to understand memory as involving processes, which advanced on prior structural ideas that conceptualized memory as traces that are searched for and found (engram; Semon, 1904), or comprised of information that is transferred between multiple memory storage systems (modal model of memory; Atkinson and Shiffrin, 1968). At the same time, this framework did not claim that memory is characterized solely by processes. In order to remember an experience, the initial encoding of an event needs to have effected a change in the brain that persists until remembering occurs. But rather than being a snapshot of the original event, the change can more likely be characterized as a modification of the cognitive system, such that when the event recurs, the resulting processing operations are interpreted both in terms of the current event and in the terms of the brain changes caused by its original occurrence (Craik, 2002).

The other main contribution of the Craik and Lockhart (1972) paper was to conceptualize memory as reflecting the initial encoding processes of perception and comprehension, such that deeper processing was associated with higher levels of subsequent remembering. Initially, this "levels-of-processing" framework viewed the success of initial encoding processes as dependent

on a progression through increasingly deeper "levels" of analysis, from "shallow" perceptual analyses such as surface form, color, loudness, and brightness, to "deeper" conceptual analyses of meaning, inference, and implication. However, a series of experiments conducted by Craik and Tulving (1975) showed that depth of encoding is not the only critical factor. Namely, they found that that a second index of processing, elaboration, was necessary. One demonstration of this was that congruent question-word combinations (e.g., "Rhymes with Spain?" TRAIN) were better encoded and recognized than words that were not congruent (e.g., "Rhymes with Spain?" TIGER). Craik (2002) proposed that depth of processing referred to the qualitative type of processing carried out on the stimulus, whereas elaboration referred to the degree to which each type of processing has been enriched during encoding. One conclusion about the congruent question-word results was that the congruency yielded more elaborate memory traces, which allowed them to become more integrated with organized knowledge structures (Moscovitch and Craik, 1976) that served as effective frameworks for reconstructive memory retrieval processes. Thus, rather than progressing through a fixed set of stages of analysis (shallow to deep; Craik and Lockhart, 1972), encoding more likely unfolded in an interactive manner that involved both stimulus-driven bottom-up processing as well as conceptually driven top-down processing.

Whereas the levels-of-processing framework mainly addressed the stage of memory encoding rather than retrieval (Craik and Lockhart, 1972), later publications began to incorporate retrieval in a levels-of-processing framework. Namely, the ideas of encoding specificity (Tulving and Thompson, 1973) and transfer-appropriate processing (Morris et al., 1977; Roediger et al., 1989) provided a complementary account to that of levels-of-processing. One main conclusion of the transfer-appropriate processing account was that memory is dependent on the retrieval test, as shown by experimental data demonstrating that degree of overlap in study-test processing (i.e., conceptual vs. perceptual) was more predictive of later memory performance than the qualitative nature of study processing itself (Morris et al., 1977; Bransford et al., 1979). Additionally, it was shown that perceptual processing at encoding could yield equivalent or even superior recognition performance than conceptual processing if participants were cued with perceptual retrieval cues. More strongly stated, it could be said that the processes during encoding that lead to effective memory are dictated by the retrieval conditions under which the memory will be tested.

On the other hand, it was found that even when processing requirements were equated at encoding and retrieval (thus maximizing transfer appropriateness), depth-of-processing effects are still demonstrated (matched-transfer levels effect; Lockhart, 2002). In an attempt to reconcile, Craik (2002) proposed that initial study processing influences the qualitative nature of the memory representation, and depth of processing imbued it with corresponding potential for retrieval. While the degree of qualitative compatibility between retrieval conditions and the actual memory representation is what drives the actual realization of the memory's potential to be retrieved, deeper encoding processes do result in encoded memory traces that are potentially more memorable, given that an appropriate cue is available at retrieval (also see Lockhart, 2002).

Theoretical frameworks of episodic memory have also been articulated at the neurobiological level of explanation (Norman and O'Reilly, 2003; Rolls, 2000; Shastri, 2002). Of major importance in these models is the hippocampus, along with surrounding brain regions of the medial temporal lobe (MTL). One prominent example of the relationship between memory and regions of the MTL was the case of patient H.M., who underwent a bilateral resection of his MTL in order to control his intractable seizures (Scoville and Milner, 1957). Following his operation, patient H.M. was unable to create new declarative memories, a condition known as anterograde amnesia. One main outcome from work on H.M. is that it stimulated further investigation on animal models to further pinpoint the role of different MTL regions in episodic memory (e.g., Mishkin, 1982; Squire et al., 1988), and in the decades of work since, it is now nearly universally accepted that structures of the MTL play essential roles in episodic memory formation (see Ranganath, 2010 for a review).

In addition, more recent work in the past several decades has focused on the interaction between the MTL and other neocortical regions in generating episodic memories. Evidence of memory impairment in patients with frontal cortical lesions (Kopelman, 2002 for a review) has prompted the conclusion that frontal lesions compromise the executive or control functions necessary for coordinating attention toward task-relevant aspects of a learning episode. In addition, neocortical regions are thought to form the substrate of our internal model of the structure of the environment (Norman, 2010). Neurobiological models of episodic memory have framed the interaction between the MTL and neocortical regions in terms originally outlined in

the principle of transfer-appropriate processing. In such models, retrieval of a recent event is thought to occur when a pattern of cortical activity corresponding to the event is reinstated by activation of a hippocampally stored representation of that pattern. Thus, anatomically distinct cortical regions that were active during the online processing of an event will also be co-activated during its retrieval, preserving the associations between the different components of the event that make it distinct from other similar occurrences.

The theoretical framework that guides the current research comes from the integration of the influential frameworks outlined above, leading to an account of episodic memory encoding that can be framed at the explanatory level of cognitive neuroscience. The key concepts that arise from these frameworks are that memory retrieval involves the recapitulation of processes and representations that were active during memory encoding, and that the likelihood of successful retrieval is a function of the extent to which the processing engaged by a retrieval cue overlaps with that engaged at encoding (Rugg et al., 2008). The studies to be described in this dissertation focus on the memory encoding aspect.

1.1.2 Cognitive neuroscience approaches to studying episodic memory encoding

1.2.2.1 Subsequent memory procedure

Within the field of cognitive neuroscience, an important method used to elucidate the neural processes that support episodic memory encoding has been the "subsequent memory" procedure (Paller and Wagner, 2002). Originally applied to electroencephalographic (EEG) data (Paller et al., 1987; Sanquist et al., 1980; Rugg et al., 1995), and later employed with functional magnetic resonance imaging (fMRI; Wagner et al., 1998; Brewer et al., 1998), the subsequent memory procedure permits the identification of neural correlates of encoding processes that predict successful memory on a later retrieval test. The logic of the procedure is as follows: 1) brain activity elicited during a series of study trials is acquired; 2) memory for information encoded in the study trials is later tested; and 3) the brain activity elicited at study is backsorted according to performance on the subsequent memory test. Subsequent memory effects, also termed differences due to memory effects (DM effects; Paller et al., 1987), refer to neural activity that differs between later remembered and not-remembered items. Subsequent memory

effects are taken to be neural correlates of differences in the efficacy of encoding, and regions exhibiting these differences are regarded as candidate loci of operations supporting successful encoding (Rugg et al., 2015).

In the past decade, much work has been conducted to elucidate the functional significance of subsequent memory effects. Specifically, why do some regions increase their activity in response to events that are later remembered? Since the inception of the subsequent memory procedure, evidence has suggested that subsequent memory effects are localized to regions involved in the online processing of different features of the remembered event. Additionally, it has been proposed that the more that attentional resources are directed to the processing of study items, the more the activity in cortical regions supporting those resources will increase, as reflected by the magnitude of subsequent memory effects in those cortical regions (Uncapher and Rugg, 2009). In reference to the theoretical frameworks outlined above, subsequent memory effects index the likelihood that the cortical activity engaged by the processing of that feature will form part of a hippocampally-mediated, offline representation of the event (Rugg et al., 2015).

1.2.2.2 Neuroimaging approach: fMRI

Studies of memory encoding were among the first to use functional neuroimaging (PET) to study the neural correlates of cognitive processing. Initially employing "blocked" experimental designs, which operationalized the neural correlates of encoding in terms of comparisons between blocks of study tasks that yielded relatively good vs relatively poor levels of memory performance, neuroimaging studies of memory encoding eventually came to favor the event-related "subsequent memory" approach, which sought to identify brain regions where within-task item-related activity predicted successful memory on a later retrieval test. This offered an advantage over blocked designs, as the "memory effects" identified by contrasting different task manipulations could have been influenced by any number of cognitive operations that were modulated by the task manipulation, rather than being specifically correlated with differential encoding activity. In addition, task-based designs were unable to address the question of what modulates the efficacy of encoding of events that seemingly engage the same cognitive processes, but to a differential degree such that there are subsequent differences in memory.

Based on prior studies, it is not thought that there is a cognitive system uniquely dedicated to memory encoding (for a review, see Rugg et al., 2015). Of all the regions that have demonstrated subsequent memory effects, only the hippocampus has been consistently identified across studies, which is in line with both human and non-human primate lesion work that has shown the hippocampus to play a central role in episodic memory encoding (see previous section). The cortical activity that comprises these patterns, however, is different depending on the types of processes that are engaged during the experience (Rugg et al., 2008; Craik and Lockhart, 1972). This is in contrast to episodic memory retrieval, where evidence from numerous studies converges to suggest that there is a set of regions that comprise a "core" recollection network that is engaged when recollection is successful, and which is insensitive to how memory is cued, or the nature of the recollected content. This network is assumed to interact with content-sensitive cortical regions (Rugg et al., 2015), in order to instantiate consciously accessible episodic representations.

Evidence supporting the theoretical framework that forms the basis of this research comes from fMRI studies where the study processing was varied, either through a task manipulation (e.g., semantic vs. phonological; Otten and Rugg, 2001), use of different study materials (e.g., visual vs. auditory words; Gottlieb et al., 2010), or contextual features (e.g., color and location; Uncapher et al., 2006). In Otten and Rugg (2001), participants made either a semantic or phonological judgment on a series of study words, and items that were later recognized with high confidence on a subsequent memory test elicited greater cortical activity than those that failed to be recognized. Crucially, the loci of the subsequent memory effects differed according to the study task; whereas the semantic task subsequent memory effects were found primarily in medial and left inferior frontal cortex, phonological subsequent memory effects were found primarily in posterior cortical regions, with the exception of the right prefrontal cortex. Furthermore, the subsequent memory effects for each task overlapped with regions that were selectively involved during engagement of each task: fMRI signals were greater for words from the animacy task in regions that included the medial frontal gyrus, central extent of the left inferior frontal gyrus and left parahippocampal cortex, whereas greater activations for words from the syllable than animacy tasks were found in the dorsal extent of the

left inferior frontal gyrus and bilateral posterior parietal and occipital regions. In an experiment where study processing was varied according to sensory modality (Gottlieb et al., 2010), participants studied pictures of objects, each paired with the object's name that was either presented visually or auditorily. During the later memory test, participants had to judge between studied and unstudied pictures, and for studied pictures indicate whether its name had been presented visually or auditorily. Visually-selective subsequent memory effects that overlapped with regions selectively responsive on visual vs. auditory study trials were identified predominately in regions within bilateral fusiform cortex and intra-parietal sulcus. An overlap between auditory subsequent memory effects and auditorily selective regions was identified in the right middle superior temporal sulcus. Finally, whereas all of the studies just reviewed utilized univariate measures of encoding activity, Gordon et al. (2014) exploited multivariate techniques and related classifier-derived measures of cortical representational strength and hippocampal activity at encoding and retrieval. These findings, along with many others (Kim, 2011), demonstrate that the distinction between processes supporting the online processing of an event, and those supporting its encoding into memory, are not honored at the cortical level (Rugg et al., 2015).

1.2.2.3 Electrophysiological approach: EEG/ERP

As mentioned earlier, prior to the advent of the use of the subsequent memory procedure in fMRI studies, the procedure was developed and used in research with event-related potentials (ERPs; Rugg et al., 1995; Sanquist et al., 1980), which are electrical potentials generated by the brain that are related to specific internal or external events (Luck, 2014). Underlying this measure of interest is the electroencephalogram (EEG), which is a measure of the electrical activity of the brain, plotted as changes in voltage over time (Berger, 1929). In its raw form, the EEG comprises a conglomeration of dozens of different neural sources of activity, of which researchers are mainly interested in the subset of neural responses associated with specific sensory, cognitive, and motor events (Luck, 2014). Although it is possible to directly observe neural activity that is *evoked* by the presentation of stimulus events (e.g., sensory ERPs occurring within the first 100ms following a stimulus), as has been the focus of numerous studies of mammalian electrophysiology in the 1940s and 50s, most studies in human electrophysiology

today rely on a signal-averaging technique in order to extract fluctuations in neural activity that are *invoked* by the psychological demands of the situation (e.g., those that reflect memory processes; Donchin et al., 1978). The signal-averaging technique involves combining multiple EEG epochs (time-locked to multiple events) together to form an average ERP waveform. This waveform appears as a series of positive and negative peaks that vary in polarity, amplitude, and duration, depicting the changes in scalp-recorded voltage over time that reflect the sensory, cognitive, affective, and motor processes elicited by a stimulus. One final point to make before delving into a review of the episodic memory encoding ERP literature is that, when observing an ERP waveform, there is a distinction between these ERP peaks (local voltage maxima), and ERP components (discrete intracranial sources of voltage that reflect specific neurocognitive processes): ERP peaks do not themselves map onto distinct ERP components in a one-to-one manner, and each peak in the waveform is usually determined by multiple separate ERP components. In order to best operationally identify and define an ERP component, one should take a converging evidence approach that combines various factors (including by not limited to polarity, latency, scalp distribution, and sensitivity to experiential manipulations) that would be expected to be true of a given process in a given context (Kappenman and Luck, 2012; see also, Rugg and Coles, 1995).

In a typical ERP study involving the subsequent memory procedure, EEG is recorded while the participant is performing a task that involves the processing of a series of items. Later on, the participant is tested on the studied items, and the activity elicited during the encoding of each item (and/or some feature associated with that item) is averaged according to whether or not the item was remembered on the subsequent memory test. As described earlier, subsequent memory effects are identified by the differences between the neural activity associated with studied stimuli that are subsequently remembered and those that are forgotten (Paller et al., 1987). Within the context of EEG, these difference waves are assumed to isolate ERP components that reflect the online processing that takes place while the participant is performing the memory task.

Why use ERPs to study memory? Unlike fMRI, which identifies subsequent memory effects in the form of brain regions that are co-activated with an event, ERP subsequent memory

effects do not provide much spatial information. This is because it is difficult to relate the ERP waveform at a particular electrode site to the neural tissue directly below the site; a large reason being that, although electrical activity can travel from the brain to the surface of the scalp, the electrical resistance of the skull is high compared to that of the underlying brain tissue, causing the voltage to spread laterally as it travels (Luck, 2014; but see also Kappenman and Luck, 2011, for a discussion of other approaches used to define ERP components, including source localization techniques in which a component is defined as activity arising from a region of cortex). The usefulness of the ERP approach comes from the fact that it provides a direct, instantaneous, millisecond-resolution measure of neural activity (Luck, 2014), such that an ERP effect observed at 150ms post-stimulus presentation reflects neural processing that occurred at 150ms post-stimulus presentation. This affords us a feature that cannot be obtained from fMRI, which provides a blood oxygen level-dependent (BOLD) signal that is a delayed, secondary consequence of neural activity. Although local blood oxygenation changes are clearly correlated with changes in synaptic activity, the chain of events that links the two is complex (Logothetis, 2008). For instance, fMRI data could be complicated by changes in the brain vasculature that may be separate from underlying neural changes. ERPs can in principle be used to place an upper bound on the temporal onset of a particular cognitive process and to index distinct computations that are separated by only a few tens of milliseconds. In contrast, the temporal resolution of fMRI is limited ultimately by the fact that the sluggish hemodynamic response acts as a low-pass temporal filter of neural activity (Wilding and Ranganath, 2011). The response time of the cerebral vasculature (Friston et al., 1994) sets a physiological limit on the temporal resolution that can be achieved, as it is too coarse to track cognitively related neural activity in real-time. Thus, ERPs are especially useful for providing a dynamic characterization of mental processes, such those involved in the encoding of episodic memories; since memory encoding involves a large number of distinct computations with overlapping timecourses (Wilding and Ranganath, 2011), the ability to collect data with real-time temporal resolution is critical. One could for instance examine the relative timing of ERP effects, as they can provide critical insights into the functional significance of any activity differences that are observed. In addition, an ERP component's scalp distribution (i.e., the pattern of voltage gradient over the scalp at any

point in time) can be used to visualize activity patterns across the scalp; additionally, scalp distribution differences can be quantified via topographic analyses to determine if differences in topographic maps are significant (Friedman and Johnson, 2000). It is generally assumed that ERP effects that differ from one another in their relative amplitudes, but not in their scalp distribution patterns, signify variations in the levels of activation of the same functional states/processes, and if any topographic differences were found, one could conclude that functionally distinct processes had been identified. However, it is crucial to keep in mind that differences in ERP scalp differences may not always signify the engagement of qualitatively different cognitive processes, as these differences may be sensitive not only to differences in *identity* of the cognitive operations, but also to the *content* of the cognitive operations (Rugg and Coles, 1995).

In the first study to employ the subsequent memory procedure with EEG (Sanquist et al, 1980), more positive-going ERPs were identified for words that were subsequently recognized than unrecognized, a pattern that has been replicated in numerous subsequent studies reporting subsequent memory effects. In a review of ERP studies of memory encoding (Rugg, 1995), the subsequent memory effect for remembered vs. not remembered items has taken the form of a sustained, frontal maximum wave in some studies, while in others the effect was evenly distributed over the midline, or demonstrated a posterior maximum. Furthermore, these effects onset as early as 300-400ms post-stimulus, and are sustained for several hundred milliseconds.

Since these early ERP findings, it has been shown that neural activity predicting subsequent memory varies with the type of stimulus encoded and how it is encoded. For example, Otten and Rugg (2001) demonstrated that the neural correlates of successful episodic encoding differed according to the nature of the study task. Participants were cued to make either animacy or letter-order judgments about visually presented words, before completing a surprise recognition memory task. Remembered words associated with the letter-ordering task elicited relatively more negative-going ERPs than forgotten words, whereas differences between remembered and forgotten words reversed in polarity for those encountered in the animacy task, both beginning shortly after word onset. These results suggest that the neural correlates of

memory encoding differ qualitatively, rather than quantitatively, according to the nature of the study task.

In a more recent study (Angel et al., 2013), participants studied two lists of words, and were instructed to memorize the words and the list in which they were presented. At test, they performed a word-stem completion task, and then judged whether their completion corresponded to an "old" or "new" word, and then indicated the list in which the items judged "old" occurred (list 1 or 2). Participants were asked to refrain from answering if they could not remember the list. This allowed for the separate identification of subsequent memory effects for successful cued recall and for successful source retrieval, allowing the authors to address the question of whether there is a "core" pattern of encoding-related activity predicting successful recollection, or if there would be differences in the scalp distribution of these two subsequent memory effects, suggesting that successful cued recall and source memory are supported by at least some distinct encoding processes. The authors identified a significant cued recall subsequent memory effect, with more positive-going ERPs for recalled items attracting incorrect source judgments than subsequently unrecalled items, but only at parietal sites, from 400 to 1200ms. Secondly, greater positivity for correct than incorrect source judgments was found specifically in frontal scalp sites between 400 and 1400ms; this long-lasting frontal modulation was specific to successful source memory, and was not found for successful cued recall. The authors interpreted this frontal subsequent memory effect as reflecting the additional study processes required to support subsequent successful source memory retrieval, such as binding processes that allow for the item and the list to be formed into a cohesive memory representation. However, it should be noted that since correct source judgments were contingent on remembering the item, and participants could not make source judgments on unrecalled items, this is a single and not double dissociation. Finally, the greater positivity for correct than incorrect source judgments is also consistent with neuroimaging studies that have identified frontal subsequent memory effects for source memory (e.g., Ranganath et al., 2004; Staresina and Davachi, 2006; Blumenfeld et al., 2011; Duarte et al., 2011), although across fMRI studies, frontal source subsequent memory effects are relatively uncommon next to frontal associative subsequent memory effects (see

following section).

1.2 Encoding episodic memory associations

1.2.1 fMRI studies of encoding episodic memory associations[1]

A key feature in forming episodic memories is the establishment of associations between the different components that comprise the memory episode (Tulving, 1983), such as the "what" (e.g., "what things were present, and which of those interacted?"), the "where" (e.g., "where did events take place?"), and "when" (e.g., when did the events take place?"). Studies investigating the neural correlates of encoding of episodic memory associations (e.g. Cansino et al., 2002; Sperling et al., 2003; Jackson and Schacter, 2004; Ranganath et al., 2004; Prince et al., 2005; Staresina and Davachi, 2006; Chua et al., 2007; Park and Rugg, 2008; Blumenfeld et al., 2011; Gottlieb et al., 2012; for a review, see Kim, 2011) have focused mainly on associations formed between two or more items belonging to a study event (item-item associations, or "associative" memory), or between an item and one or more contextual features (item-context associations, or "source" memory). In addition, studies have examined how people form memories for temporal associations (see Ranganath and Hsieh, 2016 for a review), such as those giving rise to information about the order in which events occurred (Qin et al., 2007; Staresina and Davachi, 2009; Jenkins and Ranganath, 2010; Ezzyat and Davachi, 2011; Tubridy and Davachi, 2011; Ezzyat and Davachi, 2014).

As alluded to earlier, it is not thought that there is a common network of regions dedicated to the encoding of episodic memory associations. Rather, the cortical regions involved in the successful formation of memory associations are dependent on the type and content of the associations being encoded. Take for example, the study conducted by Gottlieb et al. (2010), in which participants underwent fMRI scanning while studying a series of visually presented

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[1] This section is closely based on the contents of a previously published study: Wong, J. X., de Chastelaine, M., & Rugg, M. D. (2013). Comparison of the neural correlates of encoding item-item and item-context associations. *Frontiers in Human Neuroscience*, *7*(436), 1–12.

pictures, each of which co-occurred with either a visually or an auditorily presented name. As described above, subsequent memory effects were identified not only for correctly recognizing the picture itself in a subsequent test, but also for recollecting whether the picture's name was presented in a visual or auditory modality. Notably, the dissociation between encoding either visual or auditory information was predicated on the *associations* that were processed between the study item (in this case, the picture), and its different study contexts (in this case, either a visual or an auditory label). Additionally, the authors identified subsequent source memory effects that were insensitive to the modality of the picture's name, in bilateral inferior frontal gyrus, bilateral fusiform cortex, left posterior intra-parietal sulcus, and left anterior MTL.

In a quantitative meta-analysis of fMRI studies reporting subsequent memory effects (Kim, 2011), a distinction was made between those studies that used "item-memory" tasks, and those that used "associative memory" tasks, the latter of which involves remembering both an item and some information associated with the item. Across a variety of different study materials and tasks, it has consistently been reported that successful encoding of associative information, relative to just item information, involves more robust activity in the medial temporal lobe (MTL), including the hippocampus, due to the critical role of the MTL in episodic encoding as binding and associating internal representations linked to an event (see Chapter 1; for review, see Brown and Aggleton, 2001; Eichenbaum et al., 2007; Kim, 2011; for an updated meta-analysis of encoding-related hippocampal subsequent memory effects, see Kim, 2015).

Another finding from the Kim (2011) meta-analysis was that, compared to studies employing an item-memory task, those using an associative encoding task identified greater subsequent memory effects in the left inferior frontal cortex (LIFG), which was attributed to the greater demands of processing associations between of multiple pieces of information (Badre and Wagner, 2007; Buckner et al., 1999). One major caveat to this finding, however, was that this meta-analysis did not distinguish between studies using different types of associative encoding tasks. As described in the following section, associative encoding has been investigated in at least three categories: item-item, item-context, and temporal order associations. Thus, although the LIFG was identified as playing a role in associative encoding, as demonstrated by the meta-analysis of numerous studies employing different types of associative information, it was unclear

whether this cortical region would show differential involvement in encoding one type of association relative to another. On the other hand, if the LIFG did not show differential involvement across different types of associative encoding tasks, it would be a departure from previous research (see Kim, 2011 and Kim, 2015 for meta-analyses) that has suggested that the hippocampus (and possibly surrounding MTL) is the only brain region that demonstrated a subsequent memory effect common to different types of encoded information. Additionally, it would be a departure from studies that have suggested that the loci of subsequent memory effects in the cortex depended on the type of information being encoded (see Rugg et al., 2015 for a review).

1.3.1.2 Item-item and temporal order associations

In order to address the question of whether the LIFG serves a general role in encoding all types of associative information, one would require a study that directly compared the neural correlates of encoding different types of associations within a single study episode, and tested whether the presence of a subsequent memory effect in the LIFG would dissociate between encoding one association as compared to the other. This was part of the motivation for Experiment 1 (Chapter 2), in which we investigated the fMRI neural correlates of encoding item-item and temporal order associations within a single study episode.

While the encoding of item-item and item-context associations have been investigated in numerous human fMRI studies (e.g. Cansino et al., 2002; Sperling et al., 2003; Jackson and Schacter, 2004; Ranganath et al., 2004; Prince et al., 2005; Staresina and Davachi, 2006; Chua et al., 2007; Park and Rugg, 2008; Blumenfeld et al., 2011; Gottlieb et al., 2012; for a review, see Kim, 2011), fewer studies (as of when Experiment 1 was conducted) have investigated the neural correlates of encoding information that supports successful later temporal order judgments (Qin et al., 2007; Staresina and Davachi, 2009; Jenkins and Ranganath, 2010; Ezzyat and Davachi, 2011; Tubridy and Davachi, 2011; Ezzyat and Davachi, 2014). Prior work has suggested that memory for temporal information may partially depend on the formation of associations between items and the contextual states in which those items were experienced (Estes, 1955; Bower, 1972; Mensink and Raaijmakers, 1989; Howard and Kahana, 2002). It was hypothesized that

these contextual states are continuously and gradually changing, such that over the course of an episode, items experienced closer in time will likely be associated with more similar contextual states relative to those experienced farther away (see Polyn and Kahana, 2008, for an updated account). As will be discussed, this model provides a mechanistic account of how the encoding of associations linking items to their contexts might support later memory for temporal information.

The focus of Experiment 1 (Chapter 2) was to directly contrast the neural correlates of encoding information that supports later temporal information with those that support encoding of item-item associations. Despite the possibility that both types of information may involve the formation of some sort of association (either between items or items and their spatiotemporal contexts), it remains to be established whether the encoding of the two classes of association do indeed involve distinct neural correlates. In particular, it is currently unclear whether the stronger involvement of the LIFG in the encoding of item-item than item-context associations extends also to the encoding of temporal information. Accordingly, the first study described below tested for information supporting both temporal and associative memory. The latter test served as a "positive control", with the expectation that LIFG subsequent memory effects would be identified for the successful encoding of item-item associations. Thus, we aimed to assess whether, under study conditions where subsequent associative memory effects were evident in this region, analogous effects were also evident for the successful encoding of information supporting later memory for time.

1.3.1.3 Item-item and item-context associations

The focus of Experiment 2 (Chapter 3) was to directly compare the neural correlates of encoding item-item and item-context associations, as another opportunity to investigate whether the LIFG serves a general role in encoding all types of association. On an informal level, this question could be addressed by comparing prior literature that has identified subsequent memory effects for item-item and item-context memory encoding. As of the time this experiment was conducted, research on item-item encoding has identified subsequent memory effects in, among other lateral prefrontal cortex regions, the middle and ventral aspects of the LIFG (e.g. Blumenfeld et al., 2011; Chua et al., 2007; Jackson and Schacter, 2004; Park and Rugg, 2008;

Prince et al., 2005; Sperling et al., 2003). Another strand of research, focused on identifying the neural correlates of the successful encoding of source memories (e.g., Blumenfeld et al., 2011; Cansino et al., 2002; Duarte et al., 2011; Gottlieb et al., 2010; Gottlieb et al., 2012; Kirwan et al., 2008; Park et al., 2008; Ranganath et al., 2004; Rugg et al., 2012; Sommer et al., 2005; Song et al., 2011; Staresina and Davachi, 2006; Uncapher et al., 2006; Uncapher and Rugg, 2009), has reported enhanced activity in regions that varied according to the nature of the contextual feature that was successfully encoded (e.g. Duarte et al., 2011; Gottlieb et al., 2010; Gottlieb et al., 2012; Uncapher et al., 2006; Uncapher and Rugg, 2009). Unlike in the case of associative encoding, however, when enhanced LIFG activity is near-ubiquitous, subsequent memory effects for source information are reported inconsistently in this region. For example, in several studies, no LIFG effects were identified (Gottlieb et al., 2010; Gottlieb et al., 2012; Kirwan et al., 2008; Park et al., 2008; Sommer et al., 2005; Song et al., 2011; Uncapher and Rugg, 2009), and LIFG effects were identified in only relatively small clusters (<20 voxels) in other studies (Cansino et al., 2002, Duarte et al., 2011; Uncapher et al., 2006).

In summary, the neural correlates of encoding of both associative and source memories has been addressed in prior fMRI studies. Consistent with a wealth of evidence implicating the MTL, and especially the hippocampus, in the encoding of arbitrary associations (Brown and Aggleton, 2001; Eichenbaum et al., 2007), encoding of both types of memory has consistently been associated with subsequent memory effects in this region. The two lines of research also converge to suggest that subsequent memory effects in neocortical regions outside of the MTL vary according to the nature of the information that is successfully encoded (See Theoretical framework of episodic memory, above; also, Rugg et al., 2008 and Rugg et al., 2015). A potential point of divergence, however, concerns the LIFG. As was noted above, whereas subsequent memory effects in this region are robust and extensive for the encoding of item-item associations across a variety of study materials and tasks, they seem to be much less in evidence when item-context associations are encoded. Although suggestive, the comparison of findings across different studies does not establish that subsequent memory effects in the LIFG are greater for associative than for source encoding. Whether this is indeed the case requires studies in which the two types of subsequent memory effect are obtained from a common study task and

are directly contrasted. At the time experiment 2 was conducted, only one prior study had been reported. In Park et al. (2012), participants encoded picture pairs while concurrently hearing the pictures' names spoken in either a male or a female voice. They subsequently undertook an associative recognition test and, in addition, were required to recall the gender of the voice that had accompanied recognized test pairs during study. subsequent memory effects in the LIFG were evident for the encoding of item-item, but not item-context associations.

Although the results for the LIFG reported by Park et al. (2012) are consistent with prior findings for associative and source encoding (see above), their interpretation is subject to two important caveats. First, there was a marked disparity in performance on the two memory tests. Whereas associative recognition performance was moderately high, source memory was almost at chance. Thus, the failure to identify LIFG subsequent source memory effects might merely have been a reflection of weak memory rather than an indication of a differential role for the region in associative versus source encoding. The second caveat involves a possible attentional confound. As is typical in studies of associative encoding, the study task required that the members of each study pair were explicitly identified and relationally processed. By contrast, the source (voice) information was not incorporated into the study task, and hence did not need to be attended. It is therefore possible that the differential LIFG subsequent memory effects reported by Park et al. (2012) for associative and source encoding are a reflection of this attentional confound.

1.2.2 EEG/ERP studies of encoding episodic memory associations

Of the studies that have used the subsequent memory procedure to examine the ERP correlates of memory encoding, some of which were reviewed in an earlier section, only a handful have investigated the encoding of either item-item or item-context associations. Weyerts et al. (1997) compared the encoding of word pairs during a non-associative or an associative study task. In the non-associative task, participants had to respond when they could associate the color white with at least one of the words of the pair (e.g., loam-swan), whereas in the associative task, participants had to relate the words of the pair with each other (i.e., if they were semantically related to each other, for example, "cellar-roof"). Word pairs encoded associatively

elicited a reliable subsequent memory effect with a right frontal maximum. However, during the test phase of this study, participants were only asked to discriminate old word pairs and new word pairs, and memory was not tested for the actual association (e.g., by having participants discriminate between identical word pairs and pairs consisting of old words from different study trials). Therefore, any subsequent memory effect isolated with the memory test does not isolate encoding specifically of the association but merely of the word(s).

A right frontal subsequent memory effect was also found in another study that recorded ERPs during encoding of "fusion" or "juxtaposition" associations between two words, with the critical contrast being between word pairs quickly retrieved compared with word pairs slowly retrieved in each associative condition (Kounios et al., 2001). Participants were presented with novel pairs of nouns and instructed to fuse or combine each pair into a single coherent concept within a brief interval. Later these same pairs were presented again, half of which were in reverse order. Participants were asked to indicate whether or not each word pair was presented in the same order as in the encoding phase, with the idea that, in principle, a fusion association should not be reversible without a change in meaning and therefore provide useful information for remembering item order, whereas juxtaposition associations are semantically equivalent in either order, so they should provide less information for remembering item order). For pairs in the fusion condition (where participants associated words that could be bound into a single coherent concept, e.g., "computer-virus"), right anterior positivity appeared in an early epoch (200-800 ms post-onset of the second word of each pair), and disappeared in a middle epoch (800-2100 ms) in favor of an effect in the left anterior electrodes. On the other hand, pairs in the juxtaposition condition (where bound words resulted in no loss of their individual identities, e.g., "pepper-salt") elicited an effect in the middle epoch that was not replaced by a left anterior effect. The presence of a left anterior effect in this study seems to suggest that the ERP correlates of associative subsequent memory are not constrained to the right frontal positivity effect found in previous studies.

Bridger and Wilding (2010) employed a paradigm in which participants viewed words presented on either the left or right side of fixation, and had to make one of two binary judgments for each word (i.e., whether they found the word pleasant, or how easy the object

denoted by the word would be to draw). Then, in two separate test blocks, participants were presented with studied and unstudied words and required to make a combined confidence/feature judgment (e.g., confident pleasantness, think pleasantness, think drawing, confident drawing). In the subsequent memory analysis, there was a polarity reversal between the subsequent memory ERPs identified for the two tasks from 900 ms onwards, indicating that qualitatively distinct encoding operations were engaged in the two cases. There was also an early subsequent memory effect that was identified in the location task only, possibly reflecting the distinction between the time courses of operations supporting subsequent memory judgments for different content types (i.e., perceptual vs. conceptual). They concluded that the positive- and negative-going subsequent memory effects reflect processes that are important for later recollection of conceptual and perceptual content, respectively.

1.3 Background summary

Taken together, the research conducted so far has provided a wealth of evidence in support of the framework that states that encoding is a by-product of experiencing an event, and that other than the hippocampus and possibly surrounding regions of the MTL, there is no set of brain regions that are consistently recruited across the encoding of different types of information. However, the uncertainty of the role of the LIFG in encoding associative information makes this region a possible candidate for supporting encoding-general processes (separate from just processing the item). Therefore, it was necessary to conduct an experiment that directly compared the encoding of different types of associative information. Evidence against the claim that the LIFG is an encoding-general region would take the form of a LIFG subsequent memory effect that was selective to the successful encoding of one type of memory association and not another. In Experiment 1 (Chapter 2), we tackled the question of LIFG selectivity via an unintentional encoding task that enabled us to later assess participant's memory for item-item and temporal order information. Episodic events typically unfold over time, and a veridical memory contains both the identity of the events being associated, as well as their temporal relationships (e.g., the order in which the events occurred). We were interested in whether memory for temporal order would involve similar cortical brain regions as those involved in the encoding of item-item information. Specifically, it is possible that memory for temporal order is

based upon the same associative processes involved in processing information that would allow for later memory for item-item information. Alternatively, the encoding of temporal information could be processed in regions that do not overlap with those involved in processing non-temporal item-item information. It is possible that people could have memory for whether an item occurred before or after its pairmate, without remembering the identity of the pairmate itself.

Next, although temporal subsequent memory effects had not been extensively investigated (at the time Experiment 1 was conducted), subsequent memory associative and source subsequent memory effects have been well investigated in numerous studies (see Kim, 2011 for review). Namely, separate sets of studies had already identified LIFG subsequent memory effects for the encoding of item-item information, and found the absence of LIFG effects for the encoding of item-context information. However, it is unclear whether this dissociation arises from the possibility that the LIFG is selective for encoding/processing one but not the other, or from the difference in task requirements or difficulty through which item-item and item-context information was initially processed (although see discussion of Park et al., 2012, above). This question forms the foundation for Experiment 2 (Chapter 3), in which we presented participants with an incidental encoding task in which they had to pay attention to item-item and item-context information, and a subsequent memory test for either one of those two types of information. Although this experiment was conducted before Experiment 1, it will be described second because it was adapted from fMRI to EEG in Experiment 3 (Chapter 4), and thus will serve as a better transition.

CHAPTER 2

NEURAL CORRELATES OF THE ENCODING OF TEMPORAL ORDER FOR EVENTS WITHIN A STUDY EPISODE (EXPERIMENT 1)

2.1 Introduction

As alluded to earlier, episodic memory refers to the remembering of specific details of prior experience (Tulving, 1972). These details include not only the context in which an item was experienced and its relation to other experienced items, but also information about the timing and order in which items were experienced (Tulving, 1972; Howard and Eichenbaum, 2013). Although memory for time is essential to distinguish unique episodic memories, only recently have studies focused on the neural mechanisms supporting temporal memory. For instance, although fMRI studies have consistently reported enhanced hippocampal activity accompanying the successful encoding of both item-item and item-context associations, across a variety of different study materials and tasks (e.g., Cansino et al., 2002; Sperling et al., 2003; Park and Rugg, 2008; Duarte et al., 2011), fewer fMRI studies have reported hippocampal engagement in temporal memory tasks. These tasks have included the successful encoding of associations linking temporally discontiguous events (Qin et al., 2007; Staresina and Davachi, 2009), subsequent memory for the temporal order of words previously studied as triplets (Tubridy and Davachi, 2010), and judging the temporal proximity of events (Ezzyat and Davachi, 2014). These findings of hippocampal engagement are in line with work on animals which indicate that the hippocampus plays a key role in the encoding of temporal information (see Wallenstein et al., 1998 for an early review; see also Howard and Eichenbaum, 2013): Animals with hippocampal impairment have difficulty on tasks that require associations to be formed between temporally discontiguous events (e.g., as in trace conditioning; Ross et al., 1984), have poor memory for sequences (Fortin et al., 2002), and impaired temporal interval estimation (Jacobs et al., 2013).

Thus, based upon prior findings (for an updated review, see Ranganath and Hsieh, 2016), we expected that successful encoding of information that supported both temporal and item-item associative memory would be associated with enhanced hippocampal activity. With respect to the pre-existing fMRI studies of temporal encoding information (Qin et al., 2007; Staresina and Davachi, 2009; Jenkins and Ranganath, 2010; Ezzyat and Davachi, 2011; Tubridy and Davachi, 2010; Ezzyat and Davachi, 2014), we specifically designed our study to be like those studies which have examined temporal memory within a single episode (Qin et al., 2007, Staresina and Davachi, 2009; Jenkins and Ranganath, 2010; Tubridy and Davachi, 2011), as opposed to memory across different episodes (Ezzyat and Davachi, 2011; Ezzyat and Davachi, 2014). As will be described further, the study of the temporal relationships between items occurring within the same episode (e.g., within the same trial) is critically distinct from the study of the temporal relationships between items occurring across different episodes (e.g., across the entire span of trials in an experiment). By examining the encoding of temporal information across- rather than within- individual episodes, there is the potential for temporal encoding effects to be confounded with memory recency effects; that is, accurate performance when judging temporal information *across* episodes could be based on a comparison of the relative memory strengths of the test items (other things being equal, items that were encoded more recently in the experiment will have the greater strength). Critically, the use of relative memory strength information could have been made in addition, or as an alternative to, the retrieval of temporal information, per se (e.g. Hinrichs, 1970; Wickelgren, 1972; Hintzman et al., 1973; Huppert and Piercy, 1978; DeVito and Eichenbaum, 2011).

Out of the fMRI studies on encoding temporal relationships which have employed a within-episode approach (Qin et al., 2007; Staresina and Davachi, 2009; Jenkins and Ranganath, 2010; Tubridy and Davachi, 2011), we were particularly interested in those that have investigated the neural correlates of encoding information supporting later memory for temporal order (Jenkins and Ranganath, 2010; Tubridy and Davachi, 2011). In one of these studies (Jenkins and Ranganath, 2010), participants were scanned while performing a task that required them to maintain the order of four sequentially presented objects over a delay. Immediately after the last object of each sequence was presented, participants made a serial position judgment as to

when a probe object (one of the four they just saw) occurred. At test, they were presented with three of the four objects from each study trial (the non-probed objects), and required to recall the order in which they had initially been presented at study. Successful encoding was associated with enhanced study activity (subsequent memory effects) in, among other regions, bilateral posterior parahippocampal cortex. In the other study (Tubridy and Davachi, 2011), participants encoded noun triplets while undergoing scanning, and were later tested on item recognition ("was this triplet studied?") and, for triplets judged old, order memory also ("arrange the three words in their original presentation order"). It was reported that successful order encoding was associated with enhanced activity in bilateral hippocampus and parahippocampal cortex.

Although the findings from the foregoing two studies are consistent with the proposal that the hippocampus supports the encoding of temporal relationships (see above), their interpretation is subject to two caveats. First, in both of the studies, temporal order encoding was intentional rather than incidental. Thus, participants were motivated to adopt explicit mnemonic strategies, such as generating a spatially ordered image, or forming inter-item semantic associations that could have indirectly supported successful order judgments. Second, in the study of Tubridy and Davachi (2011), the nature of the initial recognition memory test raises the possibility of a confound between item and order memory. Although all three words of each studied triplet were presented in the test, only one of the words required recognition for the entire triplet to be judged as studied. Therefore, for some of the triplets that went on to the re-ordering test, it is possible not all of the constituent words were recognized, increasing the probability of inaccurate re-ordering. Thus, the aggregate item memory strength of misordered triplets could have been lower than that of correctly ordered triplets, complicating the interpretation of the differences in encoding-related activity that were identified.

In the present experiment, we also investigated the neural correlates of encoding temporal order within a single study episode, with a number of specifications. Firstly, we employed an incidental encoding task so as to minimize the likelihood that participants would use explicit mnemonic strategies to facilitate subsequent order judgments. Secondly, and relatedly, the study task was non-relational, in order to reduce the likelihood that inter-item associative information could be employed to make inferences about the order in which the study items had been

presented. Finally, our temporal order test involved the presentation of only one out of the two study items from each trial, obviating the opportunity for participants to solve order judgments by comparing the relative recency or memory strength of the items, which may have otherwise occurred if they had been given the identity of the other item. Instead, we hypothesized that participants would base their order judgment upon how early or late the picture occurred within the context of each trial. Specifically, a participant would judge a picture as occurring early in the trial if the context associated with the picture was similar to the context associated with trial elements from the start of each trial (e.g., the red fixation cross; see trial schematic in Figure 2.1). Relatedly, pictures judged as occurring later in the trial would likely induce recall of contexts similar to the contexts of trial elements occurring at the end of each study trial (e.g., the second black fixation cross). This proposed mechanism is based upon what we alluded to earlier. Thus we anticipated that the neural correlates of the successful encoding of temporal order in this task might more closely resemble those for encoding item-context, rather than item-item encoding.

Finally, we sought to expand our subsequent memory analyses to identify not only positive but also negative subsequent memory effects. A number of previous studies have identified negative subsequent memory effects in relation to successful item-item and item-context encoding (e.g., Daselaar et al., 2004; Park and Rugg, 2008; de Chastelaine et al., 2011; Gottlieb et al., 2012; Huijbers et al., 2012; see Kim et al., 2011 and Uncapher and Wagner, 2009 for reviews). To our knowledge, no prior study investigating temporal order memory has reported negative subsequent memory effects. Accordingly, the present study afforded us the opportunity to investigate the presence of negative subsequent memory effects for order memory and to compare them with those linked to successful associative encoding.

2.2 Materials and methods

2.2.1 Participants

Twenty-two volunteers (10 female; age range: 18-30 years, mean = 25, SD = 4.1) consented to participate in the study. All volunteers reported themselves to be right-handed, fluent English speakers in good general health, with no history of neurological disease or other

contraindications for MR imaging. Volunteers were recruited from local academic communities and were remunerated for their participation in accordance with the human subjects procedures approved by the Institutional Review Boards of UTSW and UTD. Imaging data from one participant were not collected due to claustrophobia in the scanner. Another volunteer's data were excluded because of inadequate order memory performance (>2 SDs below the sample mean). Data are reported from the remaining 20 participants (10 female; age range: 18-30 years, mean = 24.5, SD = 3.2).

2.2.2 Stimulus materials

The critical experimental items comprised 132 pairs of color pictures, each denoting a common object. The object pairings, which differed across participants, were made on a pseudo-random basis under the constraint that there were an equal number of denoted objects where neither, one, or both of the items fit inside a shoebox (as judged by the experimenter). An additional eight pairs were employed as filler or practice items. Pictures were selected from the Hemera Photo Objects 50,000 Volume II (Hemera Technologies Inc).

Study and test lists were separately generated for each participant. The trial type to which each item pair was assigned (i.e., whether the first or second picture presented at study was used as a test cue, see below) varied randomly across participants. A study list comprised 96 critical picture pairs, along with 4 filler pairs and 24 null trials. For each participant, the study list was broken down into two sub-lists (one per scan session), each of which contained 48 critical study pairs interspersed with 12 null trials. Two filler trials were employed to buffer the beginning of each sub-list. A test list consisted of 132 pictures, along with 2 filler pictures to buffer the beginning of the list. Ninety-six of the pictures had been studied as picture pairs, and were randomly intermixed with 36 unstudied pictures.

2.2.3 Procedure

The experiment consisted of a single study-test cycle. Instructions and practice for the study task were given outside the scanner. A schematic of the study design is given in Figure 2.1. During study trials, participants viewed two pictures in succession, each presented at fixation. The beginning of the trial was indicated by a red central fixation cross ("+") presented for 500

ms. The first picture then appeared for 1000 ms, before being replaced by a black cross. After 1000 ms, the cross was replaced by the second picture for 1000 ms, which was replaced by a final black cross that remained present for 2000 ms.

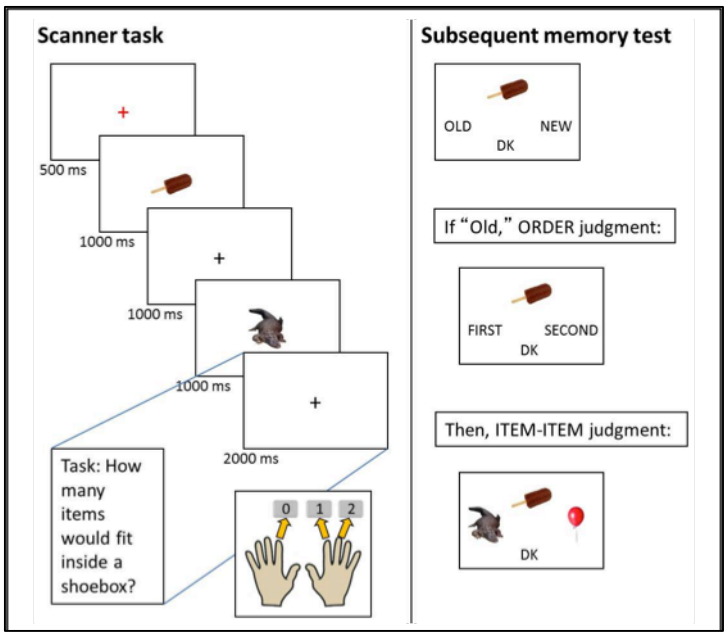

Figure 2.1. Schematic of encoding and retrieval phases of Experiment 1.

Upon presentation of the second picture in each trial, participants made one of three button presses to indicate whether zero (left index finger), one (right index finger), or both (right middle finger) of the objects denoted by the pictures fit inside a shoebox. No more than three consecutive picture pairs required the same judgment. Inter-trial interval was stochastically distributed with a minimum interval of 5.5 s modulated by the addition of approximately one-fifth the number of critical trials comprising randomly intermixed null trials (12 null trials; Josephs and Henson, 1999).

A non-scanned memory test was administered 10 minutes after the end of the final study session. The memory test took place outside of the scanner, and the study-test interval was filled by conversation with the experimenter. All 96 critical study pictures were presented, one at a time, along with 36 randomly interspersed unstudied (new) pictures. Participants were instructed to judge whether each picture was old or new and to indicate their decision using the index fingers of their left or right hand. If unsure, they were instructed to choose a third, "don't know"

(DK) option. For pictures that were judged old, order and associative judgments were then required. For the order task, the words "FIRST" and "SECOND" were presented below each picture, with the requirement to judge whether the picture had appeared first or second during its study trial. For the associative task, two previously studied pictures were presented below the picture, with the requirement to select the picture that was previously paired with the test item at study. In both tasks, a "don't know" option was also available. Of the pictures seen first in each of the 96 critical study trials, half of the pairs were used at test as test cues, and the other half as choices for the associative judgment (either as the correct pair-mate to the test cue, or as a lure picture); the same distribution applied to pictures seen second in each study trial. Thus, each picture's pair-mate served as a lure for the associative judgment of another trial. Test trials were self-paced and presented as a single block. Even when an unstudied picture was judged old, it went on to be prompted with the order and associative judgments. Thus, participants received no feedback as to the accuracy of their old/new judgment during the test. All judgments were self-paced.

2.2.3.1 fMRI scanning

A Philips Achieva 3T MR scanner (Philips Medical Systems, Andover, MA, USA) equipped with a 32 channel head coil was used to acquire both T1-weighted anatomical images (256 x 224 matrix, 1 mm^3 voxels, 160 slices, sagittal acquisition) and T2*-weighted echoplanar images (SENSE factor of 1.5, flip angle 70°, 80 x 78 matrix, FOV = 24 cm, TR = 2000 ms, TE = 30 ms). Each volume comprised 33 slices oriented parallel to the anterior-posterior commissure plane (3-mm thick slice, 1 mm interslice gap, 3 mm isotropic voxels) and was acquired in an ascending sequence. Data were acquired during the study phase in two scanning sessions, with each session comprising 180 volumes. The 5.5 s SOA allowed for an effective sampling rate of the hemodynamic response of 2 Hz. The first five volumes of each session were discarded to allow equilibration of tissue magnetization.

2.2.3.2 fMRI data analysis

Data preprocessing and analyses were performed with Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK), implemented in

MATLAB 2008 (The Mathworks, Inc., USA). Functional images were subjected to a two-pass spatial realignment. Images were realigned to the first image, generating a mean image for each session. In the second pass, the raw images were then realigned to the session-specific mean. Correction for differences in acquisition times was performed by sinc interpolation with respect to the acquisition time of the middle slice in each volume. The images were then subjected to reorientation, spatial normalization to a standard EPI template (based on the Montreal Neurological Institute (MNI) brain; Cocosco, Kollokian, Kwan, Pike, and Evans, 1997) and smoothing with an 8 mm FWHM Gaussian kernel. The functional time series were concatenated across sessions.

For each participant, study activity was modeled with a 2.5s duration boxcar function that began with onset of the first picture. The predicted blood oxygen level dependent (BOLD) response was modeled by convolving the neural functions with a canonical hemodynamic response function. The principal analyses were confined to four events of interest (non-orthogonal, see reasoning in next few paragraphs): trials on which participants correctly remembered the order of a recognized picture (order correct), trials on which the picture was recognized but the order was not remembered (order incorrect), trials on which participants remembered the recognized picture's pairmate (associative correct), and trials on which they recognized the picture but could not remember the pairmate (associative incorrect). Of the participants included in each analysis, the great majority had too few trials in the "order DK" and "associative DK" response categories (i.e., <10 trials) to allow for stable estimates of the associated neural activity. Therefore, these DK trials were collapsed with the order incorrect and associative incorrect trials, respectively. Events of no interest were modeled separately, and included filler, null, and missed/multiple button press trials. In addition, six regressors were employed to model movement-related variance, and session-specific constant terms were employed to model mean image intensity in each of the two sessions.

The functional timeseries was highpass-filtered to 1/128 Hz and scaled within-session to yield a grand mean of 100 across voxels and scans (the default settings within SPM; http://www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf). Parameter estimates for the events of interest were estimated using two different General Linear Models (GLMs) for each participant. One

GLM was employed to estimate subsequent order memory effects, whereas the other estimated the subsequent associative memory effects.[2] Common subsequent memory effects were sought by inclusively masking the associative and order subsequent memory contrasts. 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 Restricted Maximum Likelihood (ReML).

The subsequent memory contrasts for order and associative memory were carried forward to two separate group-wise analyses. For the analysis of order memory, order correct study trials were contrasted with order incorrect trials, to identify positive memory effects, whereas the reverse contrast (i.e., incorrect > correct trials) was used to identify negative order subsequent memory effects. The analogous pair of contrasts was performed to identify associative memory effects. Protection against Type I error was effected by using the "Analysis of Functional Neuroimages" (AFNI) AlphaSim tool (http://afni.nimh.nih.gov/afni/AFNI_Help/AlphaSim.html) to estimate the minimum cluster size necessary for a cluster-wise corrected significance level of $p < .05$ at a height-threshold of $p < 0.005$ (although cf. Eklund et al., 2016).[3] The critical value was 47 contiguous voxels. In light of our pre-experimental prediction that order subsequent memory effects would be identified in the hippocampus, AlphaSim was also used to estimate the voxel extent threshold within a manually drawn mask restricted to the bilateral medial temporal lobe (MTL). The critical value for this mask was 17 voxels.

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[2] Since each test item was queried for both order and associative information, analyses were initially constructed as in Gottlieb et al. (2012) such that trials remembered for "order only," "associative only" and "both" could be entered in a single design matrix. However, there were not enough trials in each category.

[3] The procedure used to compute the cluster extent threshold in this study had assumed that the smoothness distribution across brain voxels follows a Gaussian shape, which has since been found to underestimate the number of contiguous voxels needed for a certain significance threshold (Eklund et al., 2016). However, as can be seen in Table 2.2, the cluster extent of the effects of most theoretical interest to our study far exceed the minimal cluster extent value that was required.

2.3 Results

2.3.1 Behavioral performance

2.3.1.1 Study task

Mean accuracy on the study task was 0.80 (SD = 0.05). Study RTs are shown in Table 2.1. segregated according to later memory performance. A one-way ANOVA revealed no significant differences in RT between the four subsequent memory conditions ($F < 1$).

Table 2.1. Mean reaction times (ms) for correct judgments at study segregated by subsequent memory (SD in parentheses).

Subsequent memory judgment	Reaction time (ms)
Order correct	1314 (282)
Order incorrect/DK	1213 (412)
Associative correct	1321 (274)
Associative incorrect/DK	1266 (386)

2.3.1.2 Retrieval task

The item hit rate was 0.76 (SD= 0.11) against a false alarm rate of 0.05 (SD= 0.09). Conditionalized on accurate item recognition, the proportions of accurate order and associative judgments were 0.66 (SD = 0.12) and 0.52 (SD = 0.1), respectively. Following prior studies (e.g., Gottlieb et al., 2012, Wong et al., 2013), the probability of recollecting order and associative information was estimated with an index derived from a single high-threshold model, in which the probability of recollection was computed as $p(\text{recollection}) = \{p(\text{Hits}) - 0.5[1 - p(\text{DK})]\} / \{1 - 0.5[1 - p(\text{DK})]\}$. Order and associative memory estimates were 0.43 (SD = 0.17) and 0.16 (SD = 0.1), respectively. Pairwise contrasts revealed that both performance estimates were significantly greater than the chance value of zero ($t(19) = 11.53$, $p < 0.001$, and $t(19) = 6.75$, $p < 0.001$ for order and associative judgments, respectively), but that associative memory judgments were significantly less accurate than the order memory judgments ($t(19) = 5.62$, $p <$

0.001). The correlation between performance on the two memory tests was not significant (r = -0.25, p = 0.28).

2.3.2 fMRI results[4]

2.3.2.1 Positive subsequent memory effects

Positive subsequent order memory effects were identified at the whole brain level in bilateral fusiform cortex and left precentral gyrus, along with other regions illustrated in Figure 2.2 and listed in Table 2.2. Within the MTL mask, a positive subsequent memory effect was identified in the right anterior hippocampus/amygdala **(**Table 2.2**)**. Positive subsequent associative memory effects took the form of a single cluster in the ventral aspect of the LIFG (Figure 2.2. and Table 2.2).

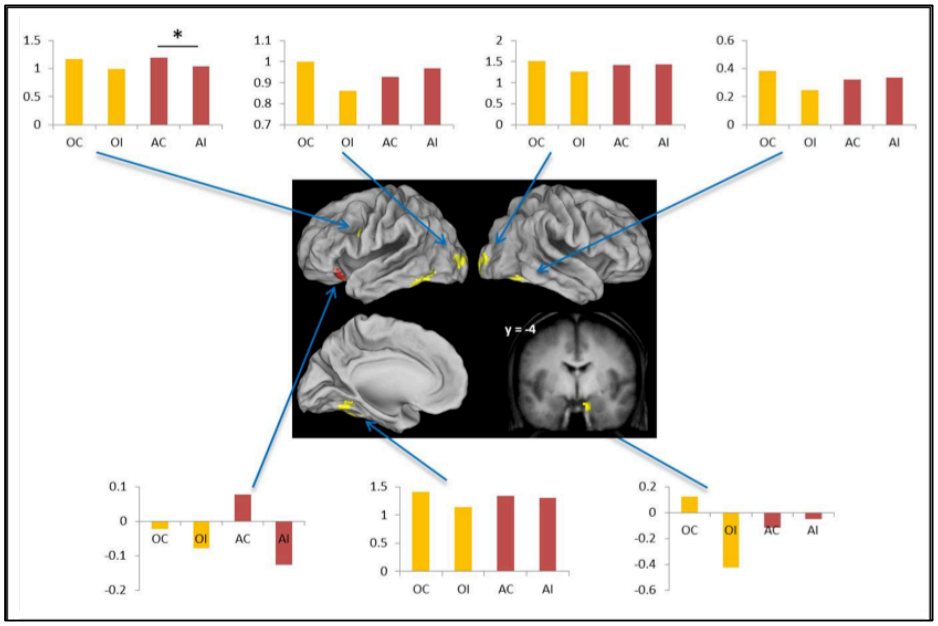

Figure 2.2. Positive SMEs for temporal order (yellow, OC = order correct, OI = order incorrect) and item-item memory (red, AC = associative correct, AI = associative incorrect).

[4] Given that we did not have sufficient trial numbers to include independent estimates of order and associative memory within the same design matrix, we could not look for common subsequent memory effects.

Table 2.2. Loci of positive subsequent memory effects.

Coordinates			Peak Z	Number of above-threshold voxels	Region
x	*y*	*z*			
Positive subsequent order memory effects, p < 0.005 at 47 voxel extent threshold					
-45	-55	-11	3.76	215	L occipital gyrus/fusiform gyrus
-48	5	28	3.64	65	L precentral gyrus
18	-97	-5	3.59	100	R occipital gyrus
36	-46	-11	3.44	121	R occipital gyrus/fusiform cortex
-24	-88	4	3.35	76	L occipital gyrus
MTL effect, p < 0.005 at 17 voxel extent threshold					
12	-4	-23	3.47	19	R anterior hippocampus/entorhinal cortex
Positive subsequent associative memory effect, p < 0.005 at 47 voxel extent threshold					
-39	32	-23	3.21	69	L orbital gyrus/inferior frontal gyrus (opercularis)

2.3.2.2 Negative subsequent memory effects

Negative subsequent memory effects were identified by performing the reverse of the contrasts described above. The resulting SPMs revealed clusters in bilateral auditory cortex, ventromedial prefrontal cortex, and right motor cortex (

Table 2.3) for the order memory contrast, and a single cluster in right superior frontal gyrus for the associative memory contrast.

Table 2.3. Loci of negative subsequent memory effects.

Coordinates			Peak Z	Number of above-threshold voxels	Region
x	*y*	*z*			
Negative subsequent order memory effects, p < 0.005 at 47 voxel extent threshold					
33	-13	67	4.28	230	R precentral gyrus
51	-19	16	3.79	197	R superior frontal gyrus/middle temporal gyrus (peak is at/near transverse temporal gyrus (Heschl's)
54	2	7	3.79	61	R inferior frontal gyrus (opercularis)
-48	-22	16	3.39	96	L transverse temporal gyrus (Heschl's)
12	41	-11	3.12	56	R orbital gyrus
Negative subsequent associative memory effects, p < 0.005 at 47 voxel extent threshold					
18	-4	64	3.37	59	R superior frontal gyrus

2.4 Discussion

The present study identified the neural correlates of encoding temporal order and item-item associations. We used a non-relational encoding task in which participants studied picture pairs, where each item was presented one after the other.

2.4.1 Behavioral findings

There were no significant RT differences between study trials according to performance on the later memory test, making it unlikely that any fMRI subsequent memory effects merely reflected differences in the efficiency with which the study events were processed. Temporal order memory was more accurate than associative memory. As our study task was intentionally constructed to prevent relational processing (see Introduction), it is unsurprising that associative memory was low. However, this difference in performance between the two tasks raises the possibility that the differences in subsequent memory effects between the two types of memory could be due to differences in memory strength. There was a weak and non-significant negative correlation across participants between temporal order and associative memory performance. This finding suggests that the processes supporting the encoding of temporal order and associative memory were at least partially independent. This is consistent with the findings, discussed below, indicating that subsequent temporal order and associative memory effects are anatomically dissociable.

What is the potential mechanism by which participants solved the temporal order judgment in the current experiment? In each scanner trial, participants incidentally encoded the order of two sequentially presented pictures; in each test trial, participants were cued with one of the two pictures and asked whether it was seen first or second during its study trial. Importantly, participants were queried about the order without being provided with any information about the identity of the other picture, making unlikely that they would base their order judgments on the relative temporal ordering or memory strength of the two pictures. Rather, it is more likely that participants judged a picture as appearing “first” or “second” based upon the initial encoding of how early or late the picture occurred within the context of each individual trial (see

Introduction). For example, if we view each study trial as a progression of items (i.e., a red fixation cross, the first picture, a black fixation cross, the second picture, and another black fixation cross, see Figure 2.1.), each of which, in turn, occurred at a specific point of the temporal context underlying the trial, then being cued with one element of the study trial (e.g., the first picture), likely induced recall of neighboring elements (e.g., the red fixation cross) via a shared temporal context.

2.4.2 fMRI findings

2.4.2.1 Positive subsequent memory effects

Positive subsequent order memory effects were identified at the whole brain level in bilateral fusiform cortex, bilateral occipital cortex, left precentral gyrus, and in the right anterior hippocampus/amygdala. The bilateral fusiform and occipital cortex effects are consistent with a prior report of subsequent order memory effects in these regions (Jenkins and Ranganath, 2010). Although the authors did not provide an interpretation for these findings (their a priori regions of interest were in the MTL and prefrontal cortex), we propose that the temporal order effects found in these regions reflect processes involved in encoding object representations. In particular, prior reports of subsequent memory effects for objects in right occipito-temporal cortex (e.g. Cansino et al., 2002; Ranganath et al., 2004; Sommer et al., 2005; Uncapher and Rugg, 2009) have been identified in the context of item-context encoding (also cf. Experiment 2). As was discussed in Gottlieb et al. (2012), it is unclear why enhanced activity in a brain region strongly implicated in object processing should facilitate the encoding of item-context associations, and in this case, temporal order information (cf. Chapter 5 General Discussion for further discussion on this matter). The MTL finding is consistent with a prior report of a subsequent order memory effect in this region (Tubridy and Davachi, 2011), a more recently published finding (Jenkins and Ranganath, 2016), as well as with previous findings implicating the hippocampus in the encoding of temporal information (see Introduction).

Positive subsequent associative memory effects took the form of a single cluster in the ventral aspect of the LIFG. There were no significant subsequent memory effects in the LIFG for order information, which is consistent with the finding that the LIFG has a stronger involvement

in the encoding of item-item rather than item-context associations, and that this selectivity extends to temporal order encoding. Furthermore, failure to identify a subsequent memory effect in the LIFG for order information suggests that the LIFG is qualitatively more involved in the encoding of item-item associations, rather than being an indication of strong memory in general. Finally, the lack of a subsequent associative memory effect in the hippocampus is inconsistent with prior findings for associative memory (see Introduction); however, given the weak performance on the associative memory test, it would be unwise to draw any conclusions about this null effect.

2.4.2.2 Negative subsequent memory effects

Negative subsequent order memory effects were identified in bilateral auditory cortex, ventromedial prefrontal cortex, and right motor cortex. The location of the auditory cortex effects is not unprecedented (Stevens et al., 2008). Increased activity in these regions are thought to reflect attention to irrelevant stimuli (in this case, scanner noise), and contribute to failed encoding in older adult participants. It is interesting to consider why these negative subsequent memory effects in the auditory cortex were present for order, but not associative encoding in the present experiment, and furthermore why these effects are not more common in prior fMRI studies of encoding. One possibility is that scanner noise was selectively detrimental to temporal order encoding because attention to an irrelevant, external context (i.e., the scanner noise) was disruptive to the process of binding items to the task-relevant internal context (i.e., the temporal context of the trial's progression), which we hypothesized earlier to be a potential mechanism underlying participants' ability to encode the temporal order of the two pictures in each trial. On the other hand, such a disruption to external context was potentially not as detrimental to the successful encoding of item-item associations.

It could be argued that the effect in right motor cortex was due to an imbalance in the use of the left and right hand to make responses. Specifically, during the study task where participants had to judge how many of the two objects would fit inside of a shoebox, they were always told to respond "0" with their left hand, and "1" or "2" with their right hand. A behavioral analysis on order performance split across these three responses showed that participants were significantly less accurate on subsequent order judgments whenever they responded with their

left hand, which likely accounts for the negative subsequent memory effect in the contralateral right motor cortex.

2.5 General conclusions

The main purpose of this study was to directly contrast the neural correlates of encoding information that supports later judgments of temporal order with those that support the encoding of item-item associations. As previously mentioned, a predominant view of temporal order encoding is based on the theory that memory for temporal information may partially depend on the formation of associations between items and the contextual states in which those items were experienced, such that over the course of an episode, items experienced closer in time will likely be associated with more similar contextual states relative to those experienced farther away. This lies in contrast to the possibility that temporal order information might be encoded via the item-item associations between two items separated in time, and characteristically involve an item-item subsequent memory effect in the LIFG.

With our present findings, while we did identify an LIFG subsequent memory effect for successful encoding of item-item information, we failed to find any evidence of the same for the successful encoding of temporal order information. Rather, successful encoding of temporal order information was associated with subsequent memory effects in the bilateral fusiform and occipital cortex, which is consistent with a prior report of subsequent order memory effects in these regions (Jenkins and Ranganath, 2010). Additionally, a subsequent order memory effect was identified in the right anterior hippocampus, consistent with the findings from a recent study which compared the neural mechanisms underlying the encoding of temporal information based on either the context or strength of encoded items or events (Jenkins and Ranganath, 2016). Whereas overall activation in the perirhinal and lateral prefrontal cortices predicted whether an object would be judged more recent, regardless of accuracy, accurate recency discrimination was predicted by changes in patterns of activation over time in the hippocampus and medial/anterior prefrontal cortices. This latter finding is relevant given the proposal of context-based models of temporal memory (Howard and Eichenbaum, 2015), which have reported that patterns of activity in rodent hippocampal neurons change gradually over time, supporting an ongoing representation of temporal context (Eichenbaum, 2013).

Level of activation in the LIFG has been found in numerous studies to make a difference as to whether two items are encoded associatively (Kim, 2011). In the current study, we have further specified the role of the LIFG to be specific to non-temporal associations between items (a conclusion that is suggested by the failure to identify subsequent memory effects for temporal order information in this region). Rather, temporal order information seems to be processed akin to the mechanism we proposed based on prior studies of temporal context memory. This dissociation between item-item and temporal order encoding has important implications for the idea that there is no single "memory encoding system" in the cortex. At the time this study was conducted, no prior studies had reported dissociable subsequent memory effects during an incidental encoding task in which participants did not explicitly pay attention to the item-item or temporal order relationships between two items. The value of the findings in this study is that they suggest that the encoding of an association between an item and its trial pairmate occurs independently of the encoding of each individual item to the temporal context in which it was experienced.

CHAPTER 3

COMPARISON OF THE FMRI CORRELATES OF SUCCESSFULLY ENCODING ITEM-ITEM AND ITEM-CONTEXT MEMORY (EXPERIMENT 2)[5]

3.1 Introduction

The aim of this study was to directly compare the subsequent memory effects that accompany the encoding of item-item and item-context associations. We employed an experimental procedure in which memory for the two classes of association could be independently assessed from a series of formally identical study trials. Importantly, we employed a study task that ensured participants directed their attention not only to the study items, but also to task-relevant contextual information. We focused on two primary questions: could any regions be identified where subsequent memory effects were common to the two classes of association? And where, if at all, would subsequent memory effects be found that were selective for associative or source encoding? We expected that the hippocampus would be among the regions to demonstrate a common subsequent memory effect (cf. Park et al., 2012). On the basis of the findings reviewed above (Chapter 1), we also expected that the LIFG would be among the regions to show a selective effect, demonstrating greater and more extensive subsequent memory effects for associative than source encoding.

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[5] This section is closely based on the contents of a previously published study: Wong, J. X., de Chastelaine, M., & Rugg, M. D. (2013). Comparison of the neural correlates of encoding item-item and item-context associations. *Frontiers in Human Neuroscience*, *7*(436), 1–12.

3.2 Methods

3.2.1 Participants

Twenty-six volunteers (12 female; age range: 18-30 years, mean = 24, SD = 4.1) consented to participate in the study. All volunteers reported themselves to be right-handed fluent English speakers in good general health, with no history of neurological disease or other contraindications for MR imaging. Volunteers were recruited from local academic communities and were remunerated for their participation in accordance with the human subjects procedures approved by the Institutional Review Board of UTSW. Three volunteers' data were excluded because there were fewer than 10 trials in one or more critical experimental conditions. An additional three volunteers' data were excluded because of inadequate memory performance (> 2 SDs below the sample mean for item recognition accuracy). Data are reported from the remaining 20 participants (10 female; age range: 18-30 years, mean = 24, SD = 3.8).

3.2.2 Experimental materials and procedures

The critical experimental items consisted of 280 color pictures of common objects, each paired with a concrete noun. There was no overlap in the objects denoted by the pictures and the words. The pairings, which were consistent across participants, were made on a pseudo-random basis under the constraints that each picture-word combination was semantically unrelated, and that for half of the pairs the object denoted by the word was larger than that denoted by the picture, and vice-versa for the remaining pairs. An additional 32 picture-word pairs were employed as filler or practice items. Pictures were selected from the Hemera Photo Objects 50,000 Volume II (Hemera Technologies Inc.), and the words were selected from the word association norms compiled by Nelson et al. (2004).

Study and test lists were separately generated for each participant. The type of trial to which each item pair was assigned (i.e., whether studied or unstudied, employed for the associative or source judgment, and study location), and the order in which the pairs were presented, varied randomly across participants. A study list comprised 200 randomly selected critical picture-word pairs, along with 12 filler pairs and 66 null trials. For each participant, the study list was broken down into three sublists (one per scan session), each of which contained 67

(66 for the third session) critical study pairs interspersed with 22 null trials. There was a 30s rest break after the 47th trial in each session. Two filler trials were employed to buffer the beginning of each scan session and rest break. A test list consisted of 280 pictures, along with two filler pictures to buffer the beginning of the list. Two hundred of the pictures had been studied as picture-word pairs, and were randomly intermixed with 80 unstudied pictures. Each studied picture, if judged old, was co-presented with two previously studied words (one of which was the picture's pair-mate), or the words, "LEFT" and "RIGHT". When an unstudied picture was judged old, it went on to be pairs either with two unstudied words, or with the LEFT/RIGHT prompts. Thus, participants received no feedback as to the accuracy of their judgments during the test. Because only half of the studied pictures were probed for their word associates, the lure words for the associative trials could be drawn without replacement from those study trials later tested for location. Thus, each studied word was presented only once at test.

The experiment consisted of a single study-test cycle (Figure 3.1). Instructions and practice for the study task were given outside the scanner, with the exception of one short practice given in the scanner to orient participants to the use of the button boxes. During study trials, participants viewed pictures, presented either to the left or right of central fixation, which were followed by a word presented at the center of the screen. The beginning of each trial was indicated by a red central fixation cross ("+") presented for 600 ms. The picture then appeared for 1000 ms, before being replaced by another black cross. After 500 ms, the cross was replaced by the word for 1000 ms, which was replaced by a final black cross lasting for 2400 ms.

The presentation of the picture served as a signal for the participant to prepare to use the hand that corresponded to the picture's location (left or right) on the screen. When the word appeared, participants used either their left or right hand (depending on the location of the picture) to indicate whether the object denoted by the picture was smaller (middle finger), or larger (index finger) than the object denoted by the word. Pictures appeared with equal frequency at each location, and no more than three consecutive pictures were presented at the same location. Each study session consisted of 67 (66 for the third session) picture-word pairs, a 30s break after the 47th trial, and four buffer trials. Inter-trial interval was stochastically distributed

with a minimum interval of 5.5 s modulated by the addition of approximately one-quarter (22) randomly intermixed null trials (Josephs and Henson, 1999).

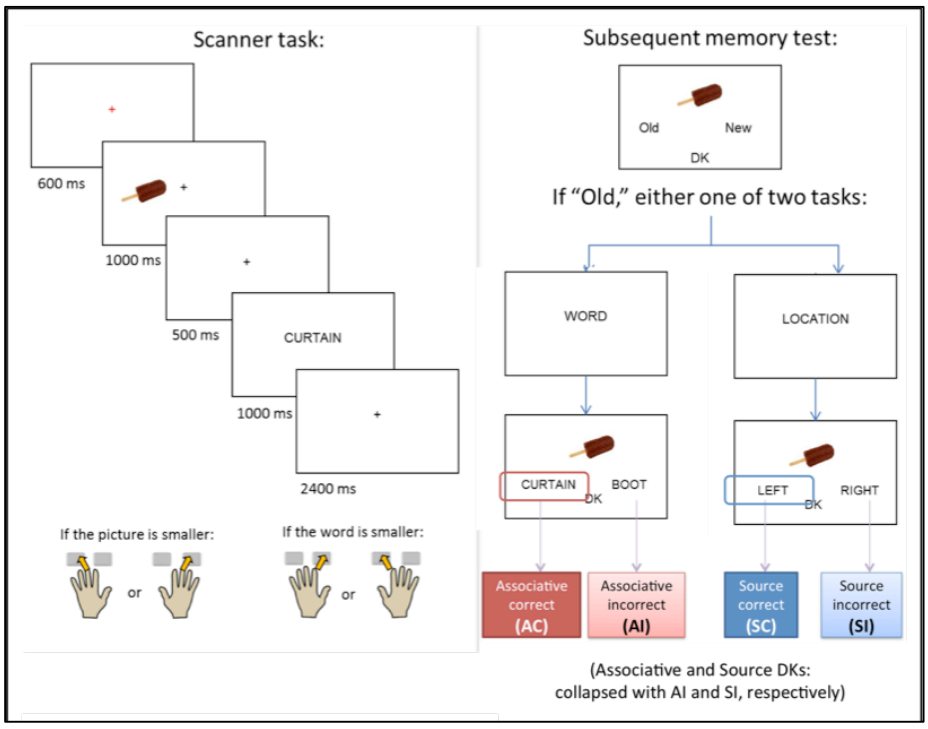

Figure 3.1. Schematic of the study and test phases of Experiment 2.

A non-scanned memory test was administered 20 min after the end of the final study session. The memory test took place outside of the scanner, and the study-test interval was filled by conversation with the experimenter. All 200 critical study pictures were presented, one at a time, along with 80 randomly interspersed unstudied (new) pictures. Participants were instructed to judge whether each picture was old or new and to indicate their decision using the index fingers of their left or right hand. If unsure, they were instructed to choose a third, "don't know" (DK) option. For pictures that were judged old, either an associative or source memory judgment was then required.[6] In the former case, two previously studied words were presented below the picture, with the requirement to select the word previously paired with the picture at study. In the

[6] Unlike Experiment 1, Experiment 2 tested only one of two memory associations from each study trial. This was to avoid overlap in test stimuli: trials testing for a picture's studied pairmate involved presenting two previously studied words, one of which was studied with another picture. Thus, half of the studied words had to be used as incorrect options at test. Pictures associated with this latter category of words were subsequently tested for location.

source task, the words “LEFT” and “RIGHT” were presented below the picture, with the requirement to select the study location of the picture. In both tasks, a “don't know” option was also available. Prior to each of the associative and source tasks, the words “WORD?” or “LOCATION?” appeared in the middle of the screen to prepare the participant for the judgment to be made. Of the pictures presented to the left of fixation at study, half appeared at test with the “WORD?” task and half with the “LOCATION?” task; the same distribution applied to pictures that appeared to the right of fixation at study. Trails testing for either associative or source memory were randomly ordered, with no more than three consecutive trials of the same type. Test trials were self-paced and presented as a single block.

3.2.3 Data acquisition

As in Experiment 1, a Philips Achieva 3T MR scanner (Philips Medical Systems, Andover, MA, USA) equipped with a 32 channel head coil was used to acquire both T1-weighted anatomical images (256 x 224 matrix, 1 mm3 voxels, 160 slices, sagittal acquisition) and T2*-weighted echoplanar images (SENSE factor of 1.5, flip angle 70degrees, 80 x 78 matrix, FOV – 24 cm, TR = 2000 ms, TE = 30 ms). Each volume comprised 33 slices oriented parallel to the anterior-posterior commissure plan (3mm thick slice, 1 mm interslice gap, 3 mm isotropic voxels) and was acquired in an ascending sequence. Data were acquired during the study phase in three scanning sessions, with the first two sessions comprising 280 volumes and the last comprising 277 volumes. The 5.5 s SOA allowed for an effective sampling rate of the hemodynamic response of 2 Hz. The first five volumes of each session were discarded to allow equilibration of tissue magnetization.

3.2.4 fMRI data preprocessing and analysis

Data preprocessing and analyses were performed with Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK), implemented in MATLAB 2008 (The Mathworks, Inc., USA). Functional images were subjected to a two-pass spatial realignment. Images were realigned to the first image, generating a mean image for each session. In the second pass, the raw images were then realigned to the session-specific mean. Correction for differences in acquisition times was performed by sinc interpolation with respect

to the acquisition time of the middle slice in each volume. The images were then subjected to reorientation, spatial normalization to a standard EPI template (based on the Montreal Neurological Institute (MNI) brain; Cocosco, Kollokian, Kwan, Pike, and Evans, 1997) and smoothing with an 8 mm FWHM Gaussian kernel. Because of the relatively small numbers of events of interest present in each separate scanning session, functional time series were concatenated across sessions.

For each participant, study activity was modeled by a 5s duration boxcar function that began with picture onset on each study trial. The predicted blood oxygen level dependent (BOLD) response was modeled by convolving these neural functions with a canonical hemodynamic response function. The great majority of participants had too few trials in the "associative DK" (mean = 4.6, SD = 4.7) and "source DK" (mean = 3.1, SD = 3.1) response categories to allow for stable estimates of the associated neural activity. Therefore, these DK trials were collapsed with the associative incorrect and source incorrect trials, respectively. The principal analyses were confined to four events of interest: trials on which participants remembered the word associated with a recognized picture (associative correct), trials for which the picture was recognized but the associated word was not remembered (associative incorrect), trials on which participants remembered the location associated with a recognized picture (source correct), and recognized pictures for which the location was not remembered (source incorrect). Item misses were modeled as a separate category. A final category comprised events of no interest, and included filler trials, null trials, and trials associated with multiple or missed button presses. In addition, six regressors were employed to model movement-related variance, and session-specific constant terms were employed to model mean image intensity in each of the three sessions.

The functional timeseries was highpass-filtered to 1/128 Hz and scaled within-session to yield a grand mean of 100 across voxels and scans (the default settings within SPM; http://www.fil.ion.ucl.ac.uk/spm/doc/manual.pdf). Parameter estimates for events of interest were estimated using a General Linear Model. 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 Restricted Maximum Likelihood (ReML).

Parameter estimates for the four conditions of interest (associative correct, associative incorrect, source correct, and source incorrect) were derived for each participant and carried forward to a second level group-wise analysis. In this analysis, individual participants' parameter estimates for the four conditions of interest were entered into a repeated-measures one-way ANOVA model, as implemented in SPM8. Planned contrasts assessing the different effects of interest were performed using the common error term derived from the ANOVA. Protection against Type I error was effected by using the "Analysis of Functional Neuroimages" (AFNI) AlphaSim tool (http://afni.nimh.nih.gov/afni/AFNI_Help/AlphaSim.html) to estimate the minimum cluster size necessary for a cluster-wise corrected significance level of $p < .05$ at a height-threshold of $p < .005$. The critical value was 47 contiguous voxels.[7] As described in the Results section, each planned contrast was inclusively masked with additional contrast(s) to identify subsequent memory effects selective for, or common to, associative or source encoding. The 47 voxel extent threshold was maintained after application of the masks. In light of our pre-experimental prediction that both source and associative subsequent memory effects would be identified in the MTL, AlphaSim was also used to estimate the voxel extent threshold within a mask restricted to the bilateral MTL. The critical value, for a corrected significance level of $p < .05$ at a height-threshold of $p < .005$, was 17 voxels.

3.3 Results

3.3.1 Behavioral performance

3.3.1.1 Study task

Mean accuracy on the study task was 0.83 (SD = 0.06). A one-way ANOVA revealed no significant differences in RT between the four subsequent memory conditions ($F < 1$; Table 3.1).

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[7] As noted in Experiment 1, the procedure used to compute the cluster extent threshold in this study was based upon the assumption that the smoothness distribution across brain voxels followed a Gaussian shape, which has since been found to underestimate the actual cluster extent necessary to reach a nominal familywise error rate of 5% (Eklund et al., 2016). However, as can be seen in Table 3.3, the cluster size of the effects of most theoretical interest to our study far exceed the nominal cluster extent value that was required.

Table 3.1. Mean reaction times (ms) for correct size/hand judgments at study segregated by subsequent memory (SD in parentheses).

Subsequent memory judgment	Reaction time (ms)
Associative correct	1509 (439)
Associative incorrect/DK	1496 (441)
Source correct	1504 (457)
Source incorrect/DK	1460 (410)

3.3.1.2 Retrieval task

The item hit rate was 0.81 (SD = 0.10) against a false alarm rate of 0.16. Conditionalized on accurate item recognition, the proportions of accurate associative and source judgments were 0.68 (SD=0.07) and 0.74 (SD=0.11) respectively. Following prior studies (e.g. Gottlieb et al., 2012), associative and source memory were estimated with an index derived from a single high-threshold model, in which the probability of recollection was computed as p(recollection) = {p(Hits) – 0.5[1 – p(DK)]} / {1 – 0.5[1 – p(DK)]}. The index was calculated separately for associative and source memory. Associative and source memory estimates were 0.40 (SD = 0.11) and 0.51 (SD = 0.20), respectively. Pairwise contrasts revealed that both performance estimates were significantly greater than the chance value of zero ($t(19) = 16.86$, $p < 0.001$, and $t(19) = 11.39$, $p < 0.001$ for associative and source judgments, respectively), and that the associative memory judgments were significantly less accurate than the source memory judgments ($t(19) = 2.35$, $p < 0.05$). The correlation between performance on the two memory tests was low and not significant ($r = 0.23$, $p = 0.33$).

3.3.2 fMRI results

3.3.2.1 Positive subsequent memory effects

3.3.2.1.1 Common subsequent memory effects[8]

To identify regions demonstrating subsequent memory effects common across associative and source recollection, the main effect of recollection (associative correct + source correct > associative incorrect + source incorrect; thresholded at $p < .005$) was inclusively masked with the separate subsequent memory contrasts for associative and source memory (associative correct > associative incorrect and source correct > source incorrect, respectively; each thresholded at $p < .05$ one-sided). Thus, the resulting SPM identified voxels where the main effect was accompanied by reliable simple effects for the constituent subsequent memory contrasts (cf. Gottlieb et al., 2012; Park and Rugg, 2011). Common effects were identified in left fusiform cortex, the left anterior hippocampus/amygdala, and the left putamen (Figure 3.2 and Table 3.2). The main effect of recollection alone (i.e. not masked with the respective simple effects) included an additional cluster in left hippocampus (peak at -30, -22, -20; Z = 3.0; 22 voxels).

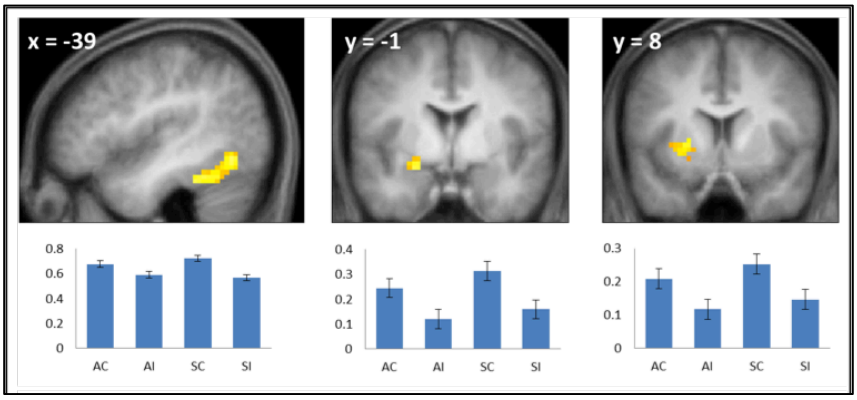

Figure 3.2. Common subsequent memory effects. Bar plots show mean parameter estimates (left to right) for the four conditions of interest (AC = associative correct; AI = associative incorrect; SC = source correct; SI = source incorrect) for peak voxels in the left fusiform (left), left anterior hippocampus/amygdala (center), and left putamen (right). Results are overlaid onto sections of the across-participants mean T1-weighted anatomical image (note – in this and subsequent figures, the mean image in derived from only 19 of the 20 included participants, because of the corruption of one participant's anatomical data). Error bars here and in the following figures signify the standard error of the mean derived from the error term of the one-way ANOVA (Loftus and Masson, 1994).

[8] In contrast to Experiment 1 (Chapter 2), common subsequent memory effects were identified in Experiment 2 because each test cue was only tested for either associative or source information, allowing all of the study trials to be independently represented in the same design matrix.

3.3.2.1.2 Selective subsequent memory effects

Subsequent memory effects selective for associative memory were identified by inclusively masking the relevant subsequent memory contrast (associative correct > associative incorrect; thresholded at $p < .005$) with the directional interaction contrast that identified voxels where associative effects exceeded source effects [(associative correct > associative incorrect) > (source correct > source incorrect)]; thresholded at $p < .05$]. Thus, the resulting SPM identified voxels that demonstrated a reliable subsequent associative memory effect that was also reliably greater than the corresponding source memory effect. The procedure identified effects throughout the extent of the LIFG, along with other regions documented in Figure 3.3A and Table 3.2**.** The analogous pair of contrasts was performed to identify effects selectively associated with the encoding of source information. These identified a single cluster in right fusiform cortex (Figure 3.3B and Table 3.2).

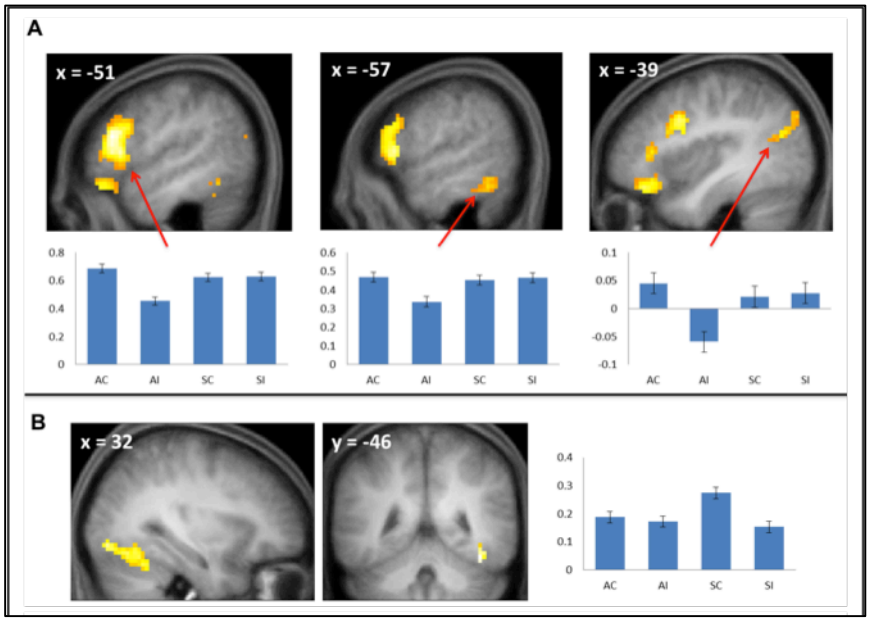

Figure 3.3. (A) Subsequent associative memory effects. Barplots show (left to right) mean parameter estimates for the four conditions of interest for peak voxels (arrows) in LIFG, left inferior temporal gyrus, and left angular gyrus. (B) Subsequent source memory effect in the right fusiform cortex. Two views of the same cluster are shown. Bar plot shows the peak parameter estimates for the four conditions of interest. Results are overlaid onto sections of the across-subjects mean T1-weighted anatomical image.

Table 3.2. Loci of subsequent memory effects for Experiment 2.

Coordinates			Peak Z	Number of above-threshold voxels	Region
x	*y*	*z*			
Common effects					
-24	-1	-14	3.85	65	L amygdala/anterior hippocampus
Subpeak					
-21	8	1	3.67		L putamen
-39	-52	-20	4.87	152	L fusiform cortex
Selective associative memory effects					
-36	35	-17	4.16	155	L orbitofrontal cortex
-51	26	22	4.99	481	L inferior frontal gyrus
-24	23	49	3.24	48	L superior frontal sulcus
-57	-52	-17	3.25	47	L inferior temporal gyrus
-39	-70	22	3.55	90	L angular gyrus
12	-82	-35	3.23	48	R cerebellum
Selective source memory effects					
42	-46	-17	4.21	167	R fusiform cortex
Common negative effects					
0	-46	58	3.84	125	Medial parietal cortex (precuneus)

3.3.2.2 Negative subsequent memory effects

Negative subsequent memory effects were identified by performing the reverse of the contrasts described above. Thus, common effects were identified by inclusively masking the relevant main effect (associative correct + source correct) < (associative incorrect + source incorrect) with the constituent pairwise contrasts (associative correct < associative incorrect and source correct < source incorrect; each thresholded at $p < .05$). The resulting SPM revealed a single cluster in medial parietal cortex (precuneus; Table 3.2 and Figure 3.4). No negative effects selective for either associative or source memory were identified.

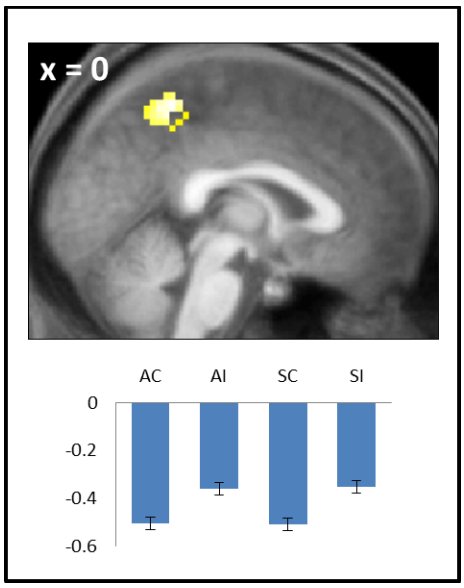

Figure 3.4. Negative common subsequent memory effect in the medial parietal cortex (precuneus). Bar plot shows the peak parameter estimates for the four conditions of interest. Results are overlaid onto a sagittal section of the across-participants mean T1-weighted anatomical image.

3.4 Discussion

3.4.1 Behavioral findings

There were no significant RT differences between study trials according to performance on the later memory test, making it unlikely that any fMRI subsequent memory effects merely reflected differences in the efficiency with which the study events were processed. Source memory was more accurate than associative memory, raising the possibility that the larger subsequent memory effect in the right fusiform that was identified for source relative to associative encoding (Figure 3.3B) may merely have reflected a difference in memory strength. Crucially, since associative memory was weaker than source memory, this potential confound cannot be responsible for the finding that several regions, including the LIFG, demonstrated subsequent memory effects that were selective for associative encoding.

There was a weak and non-significant correlation across participants between associative and source memory performance. This finding suggests that the processes supporting the encoding of item-item and item-context associations were at least partially independent. This is

consistent with the findings, discussed below, indicating that subsequent associative and source memory effects are anatomically dissociable.

3.4.2 fMRI findings

3.4.2.1 Positive subsequent memory effects

3.4.2.1.1 Common effects

Subsequent memory effects common to both types of association were identified in left fusiform cortex, the putamen, the left anterior MTL on the border between the hippocampus and amygdala and, when a less stringent criterion was applied, in the body of the left hippocampus. The findings for the anterior MTL and hippocampus are consistent with numerous prior reports of subsequent source and associative effects in these regions (e.g., Chua et al., 2007; Gottlieb et al., 2012; Jackson and Schacter, 2004; Summerfield et al., 2006; see Kim, 2011 for review). The common effect evident in left fusiform cortex likewise replicate prior findings, with respect to both source (e.g. Gottlieb et al., 2012) and associative (e.g., Chua et al., 2007; Park and Rugg, 2011) encoding (see Kim, 2011, for review).

We also identified a common subsequent memory effect in the putamen, consistent with the findings of several prior studies that reported subsequent memory effects both in the putamen and other striatal regions during episodic encoding (e.g. Adcock et al., 2006; Gottlieb et al., 2012; Park and Rugg, 2011; Prince et al., 2005; Sperling et al., 2003). It has been hypothesized (Sadeh et al., 2011) that the contribution of the striatum to episodic encoding is through its role in controlling the contents of working memory (McNab and Klingberg, 2008). In the current study, the requirements to remember which hand to use for the study judgment, as well as the identity of the study picture, likely taxed working memory. Thus, it is possible that the common subsequent memory effect in the putamen reflects the benefit to encoding that occurred when these two components of the study event were represented in working memory to the exclusion of task-irrelevant information.

3.4.2.1.2 Selective effects

The most important finding in the present study involves the selectivity of the LIFG for the encoding of associative rather than source information: whereas subsequent associative

memory effects in this region were robust and extensive, they were essentially undetectable for the encoding of source information (even at a $p < .05$ threshold, the source correct > source incorrect contrast identified only 2 voxels that overlapped with the LIFG subsequent associative memory effect). This finding is consistent with the impression gained from the prior literature (see Introduction), and with the findings of a prior study that also directly contrasted subsequent associative and source memory effects (Park et al., 2012). Unlike in that study, however, the present finding cannot be a consequence of weaker memory for source than associative information (see above), and nor can it be attributed to the absence of a requirement to explicitly attend to relevant contextual information (see Introduction).

It is possible that our finding that LIFG subsequent memory effects were selective for successful associative encoding may reflect weaker lateralization of subsequent memory effects in the inferior frontal gyrus for source than for associative encoding. By this argument, variable or weak lateralization of the processes supporting source encoding could make the effects difficult to detect, especially if, as in the present study, participants were not assessed for strength of lateralization of function beyond self-reported handedness. While it is not possible to conclusively reject this proposal, the finding that LIFG subsequent source memory effects were essentially undetectable (see above) is consistent with the view that this region did indeed play little or no role in the encoding of item-context associations in the present study.

What light do the current findings shed on the role of the LIFG in episodic memory encoding? It has been proposed that this region supports such functions as the controlled retrieval of semantic (and other) representations, and the selection among competing representations of the one most appropriate for the current cognitive context (e.g., Badre and Wagner 2007; Gold and Buckner, 2002; Thompson-Schill et al., 1997; Thompson-Schill et al., 1999). These functions are likely to be engaged in study tasks typically employed in studies of associative (item-item) encoding [e.g., whether a name provided a good fit to a face (Sperling et al., 2003); generating a “mental image” incorporating both items (Jackson and Schacter 2004); or judging which item would “fit” inside the other in (Park and Rugg, 2011)]. From this perspective, subsequent associative memory effects in the LIFG can be understood in terms of the principle that cortical subsequent memory effects reflect modulation of activity in regions engaged during

the on-line processing of a study event (Rugg et al., 2008). For example, one possibility is that relative enhancement of LIFG activity during successful associative encoding supports the generation of well-specified representations of the two study items and their task-relevant attributes, and that such representations are especially conducive to the formation of a durable associative memory.

This is not to say that the LIFG cannot also be engaged during the processing of individual study items. Indeed, subsequent memory effects in this region have been reported for the encoding of individual items since the inception of the fMRI subsequent memory procedure (Wagner et al., 1998), and are particularly prominent when items are subjected to semantically-oriented study (e.g. Otten and Rugg, 2001). Why, then, is LIFG activity not enhanced during successful source encoding, when a single item must be associated with a contextual feature (rather than another study item, as in associative encoding)? We conjecture that the absence of LIFG subsequent source memory effects reflects the fact that the formation of an item-context association usually does not require controlled retrieval and selection beyond what is needed to generate a task-appropriate representation of the item itself: typically, contextual information (for example, spatial location, color, or sensory modality) is in the form of perceptual features, the representation of which is largely bottom-up, with little need for selection among competitors. To illustrate this further, a prior study that involved encoding pictures in multiple competing contexts (4 colored borders, 4 locations) failed to identify source subsequent memory effects in the LIFG. In short, whereas the processing of two items engages the LIFG to a greater extent than does the processing of a single item, the processing of an item in association with one or more contextual features typically does not.

It might be proposed that the foregoing account can be reduced to the argument that LIFG subsequent memory effects merely reflect the level of processing to which a given component of the study event was subjected. By this argument the effects are prominent when a component is "deeply" processed (i.e. to the level of its meaning), but not when it is processed more superficially. Other findings suggest however that this is unlikely to be a sufficient explanation for the dissociation in this region between subsequent associative and source memory effects. Park and Rugg (2008) contrasted subsequent associative memory effects

according to whether the study pairs were judged for their semantic or phonological similarity (a typical depth of processing manipulation; Craik and Lockhart, 1972). As would be expected, subsequent memory performance was markedly better for the pairs from the semantic task. Nonetheless, the robust subsequent memory effects identified in the LIFG did not differ in magnitude as a function of study task (and, hence, depth of processing). These findings can be accommodated by the foregoing account if it assumed that both study tasks required resolution between potentially competing representations of each member of the study pairs (semantic representations in one case and phonological in the other).

If the foregoing account is correct, the question arises as to why subsequent source memory effects in the LIFG have sometimes been reported (e.g. Blumenfeld et al., 2011; Duarte et al., 2011; Ranganath et al., 2004; Staresina and Davachi, 2006). One possibility of course is that processing of the source feature in these studies required engagement of the LIFG. Another possibility, however, is that the LIFG effects reflect a confound between the accuracy of source memory and strength of item memory: other things being equal, the accuracy and confidence with which test items are recognized is greater for items associated with a correct source judgment than it is for items associated with an incorrect judgment (e.g., Kirwan et al., 2008; Slotnick and Dodson, 2005; Song et al., 2011). Thus, as has been argued for subsequent source memory effects in the hippocampus (Kirwan et al., 2008; Song et al., 2011; but see Rugg et al., 2012), effects in the LIFG might reflect the differential role of this region in the encoding of relatively strong versus relatively weak item memories rather than in the encoding of item-context associations.

A second region to demonstrate selective subsequent associative memory effects was ventral parietal cortex in the vicinity of the angular gyrus. Similar findings have been reported in prior studies of associative encoding (de Chastelaine et al., 2011; Park and Rugg, 2008). The angular gyrus is often held to belong to the default mode network, and typically exhibits negative rather than positive subsequent memory effects (Uncapher et al., 2011). The region is, however, heavily implicated in the processing of semantic and conceptual information (Binder and Desai 2011; Jefferies, 2013). Furthermore, it has been reported that regions within the angular gyrus that demonstrate task-related deactivation (consistent with a role in default mode processing),

and regions that are selectively active during semantic processing, are partially dissociable (Seghier et al., 2010). Therefore it seems likely that the subsequent associative memory effects identified in this region in the present and prior studies reflect the twin facts that the region was recruited in service of the demands of the study task, and that associative encoding benefited when processing of the semantic features of the items was emphasized.

The final region to demonstrate selective subsequent associative memory effects was in left inferior temporal cortex, lateral to the nearby common effect (see Figure 3.3A and Table 3.2.). It has been proposed that this region supports access to semantic knowledge of both words and objects (Binder et al., 2009; Jobard et al., 2003). Therefore, as in the case of the subsequent associative memory effect in the angular gyrus, the left inferior temporal effect may reflect the benefit to encoding that accrued when a relatively large amount of resources was allocated to semantic processing of the items.

In contrast to subsequent associative memory effects, selective source memory effects were confined to a single cluster in right fusiform cortex. This finding adds to prior reports of subsequent source memory effects for objects in right occipito-temporal cortex (e.g. Cansino et al., 2002; Ranganath et al., 2004; Sommer et al., 2005; Uncapher and Rugg, 2009). The present finding represents an advance over these previous reports in that they implicate the region in the encoding specifically of object-context associations, rather than associative encoding more generally. As was discussed by Gottlieb et al. (2012), it is unclear why enhanced activity in a brain region strongly implicated in object processing should facilitate the encoding of such associations. The present findings strengthen the evidence supporting a role for right fusiform cortex in the encoding of object-context associations, but do not further understanding of the underlying mechanism.

3.4.2.2 Negative subsequent memory effect

A robust negative common subsequent memory effect was identified in medial parietal cortex. The location of this effect is consistent with the findings of numerous prior studies in which similar effects were reported across a variety of study materials and tasks (Kim, 2011), including two prior studies of source encoding (Duarte et al., 2011; Gottlieb et al., 2012). Negative subsequent memory effects are thought to result mainly from modulation of “default

mode" activity (Buckner et al., 2008; Gusnard and Raichle, 2001), reflecting the benefit to encoding that accrues when attentional resources are fully withdrawn from internally-directed cognition and allocated to the study event (Daselaar et al., 2004; Uncapher and Wagner, 2009). Together with prior findings, the present results suggest that disengagement of default processes is beneficial for the encoding of both item-item and item-context associations.

3.4.3 General conclusions

Prior studies of memory encoding have identified LIFG subsequent memory effects for the encoding of item-item information, while a separate set of studies have failed to identify LIFG subsequent memory effects for the encoding of item-context information. However, these findings are ambiguous as to whether LIFG subsequent memory effects are selective for encoding/processing of one type of association but not the other, or if the apparent dissociation arises from differences in task requirements or difficulty through which item-item and item-context information was initially processed (see discussion of Park et al., 2013 and Introduction). The study design used in the present experiment was intended specifically to address this question by having participants incidentally encode item-item and item-context information while performing the same task on each trial; the only difference between the trials was whether they were later queried for item-item or item-context information. This maximized the likelihood that any task-related differences in subsequent memory effect would reflect differences in processing requirements for item-item and item-context processing, and not from any systematic differences in task requirements. Having been the first study to control for these factors, the current findings provide evidence against the idea that the LIFG subsequent memory effect is indexing an encoding-general process.

CHAPTER 4

EEG/ERP CORRELATES OF SUCCESSFUL ENCODING OF ITEM-ITEM AND ITEM-CONTEXT ASSOCIATIONS (EXPERIMENT 3)

4.1 Introduction

The aim of this study was to continue to directly compare the subsequent memory effects that accompany the encoding of item-item and item-context associations. Using the experimental procedure outlined in Experiment 2 (with minor adaptations for EEG, described below), memory for the two classes of association was independently assessed from a series of formally identical study trials. EEG/ERP techniques were used to more precisely characterize the temporal correlates of encoding item-item and item-context associations. Based upon the findings from the fMRI version of this study (Experiment 2; Chapter 3), we predicted that the encoding of associative and source information would elicit qualitatively different scalp distributions of subsequent memory effects, reflecting different patterns of neural activity. Based upon subsequent memory ERP studies reviewed in Chapter 1 (Otten and Rugg, 2001; Bridger and Wilding, 2010), we also predicted that there would be a dissociation in the polarity of the ERP subsequent memory effect effects, with correctly remembered associative information eliciting more positive-going ERP subsequent memory effects, and correctly remembered source information eliciting more negative-going ERP subsequent memory effects. Finally, we predicted that there would be a dissociation in when ERP subsequent memory effects appeared during each trial. Namely, source subsequent memory effects would arise soon after the onset of the picture and its location information, whereas associative subsequent memory effects would also onset at picture presentation, and be sustained until after the picture's word associate has also been presented. We would expect source subsequent memory effects to arise as soon as the source information is available (in this case, when the picture is presented on either the left or right side of the screen). Associative subsequent memory effects should also be present sometime after the picture has been presented, since the successful formation of an item-item

association between the picture and the subsequently presented word would presumably require successful encoding of the picture itself.

4.2 Methods

4.2.1 Participants

Thirty-seven [17 females; aged 18-29 yrs, mean = 22] students from The University of Texas at Dallas (UTD) participated in return for payment of $30/hr. Participants reported that they were free from neurological or psychiatric disorder, and were right-handed native English speakers. Prior to participating, all participants gave their informed consent in accordance with the UTD Institutional Review Board guidelines. Twelve participants were rejected from analysis because there were insufficient artifact-free trials (<12) in their ERPs for one or more of the critical experimental conditions. Mean age of the remaining participants (11 female) was 23 (range 18-29) years.

4.2.2 Experimental materials and procedure

As in the fMRI version of this study, the stimulus set consisted of color pictures of common objects, each paired with a concrete noun (Wong et al. 2013; see Chapter 3 for more details). The experimental procedure consisted of a single study-test cycle (four study blocks followed by a single test block). During study trials (Figure 4.1, left panel), participants viewed pictures, presented either to the left or right of central fixation, each followed by a word presented at the center of the screen. The beginning of each trial was signaled by a red central fixation cross ("+") presented for 600 ms. The picture then appeared, either to the left or right of a black fixation cross, for 1000 ms, and participants were instructed to prepare use of the hand corresponding to the picture's location (without actually making a response). The display was then blanked for 500 ms, after which the word appeared in the middle of the screen for 1000 ms, before being replaced by a final black fixation cross at center. As soon as the word onset, and throughout the duration of the final black fixation cross (2400 ms), participants had the opportunity to make a response using the middle or index fingers of either their left or right hands. Pictures appeared with equal frequency at each location, and no more than three

consecutive pictures were presented at the same location. For each participant, the study pairs were presented across four separate blocks, each of which contained 60 critical study pairs and 2 filler trials.

The study procedure just described was essentially the same as in the fMRI study, with several modifications to make it suitable for EEG. First, participants were instructed to focus on the central fixation cross at all times, to minimize the occurrence of artefactual horizontal eye movements in the EEG. Thus, the eccentricity of the picture from fixation was decreased from the fMRI version, such that the frame subtended a visual angle of 3° at a 1 meter viewing distance. Secondly, the study list was broken up into four sublists as opposed to three, with a 30s rest break halfway through each sublist, to allow participants to relax their eyes and forehead muscles. This procedure was implemented to minimize ocular and muscle artifacts that could arise from prolonged concentration on the computer screen. Finally, the last modification was that the study task was changed from "which is smaller" to "which would fit into the other." This was the result of extensive behavioral piloting that was conducted to find a task giving adequate and equal memory performance on the associative and source tasks within an EEG environment.

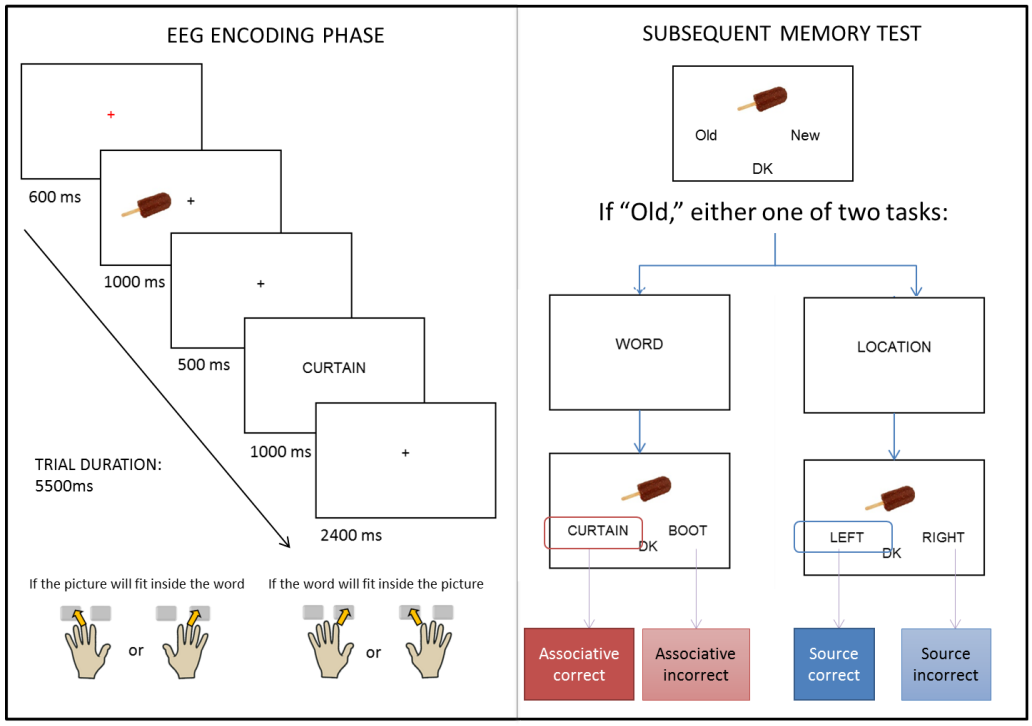

Figure 4.1. Schematic of the EEG encoding phase and subsequent memory test in Experiment 3.

Since EEG was not recorded during the memory test, the study-test interval involved removing the EEG cap and washing off the electrode gel. The memory test (Figure 4.1, right panel) was administered 15 min after the end of the final study phase, and was essentially the same test procedure used in the fMRI version of this study (see Chapter 3). During memory test trials, all 240 critical study pictures were presented, one at a time, along with 80 randomly interspersed unstudied (new) pictures. Participants judged whether each picture was old or new and indicated their decision using the index fingers of their left or right hand. If unsure, they were instructed to choose a third, "don't know" (DK) option. For pictures that were judged old, either an associative or source memory judgment was required. In the former case, two words were presented below the picture, with the requirement to select the word previously paired with the picture at study. In the source task, the words "LEFT" and "RIGHT" were presented below the picture, with the requirement to select its studied location. In both tasks, a "don't know" option was also available. Before making either judgment, "WORD?" or "LOCATION?" flashed in the middle of the screen to prepare the participant for the judgment to be made.

Note that, even when an unstudied picture was incorrectly judged old, it was still followed by either a pair-mate judgment (i.e., choosing from two unstudied words), or with the LEFT/RIGHT prompts. Thus, participants did not receive feedback as to the accuracy of their judgments during the test. Because only half of the studied pictures were probed for their word associates, the lure words for the associative trials were drawn without replacement from those study trials later tested for location. Thus, each studied word was presented only once at test. Of the pictures presented to the left of fixation at study, half appeared at test with the "WORD?" task and half with the "LOCATION?" task; the same distribution was applied to pictures that appeared to the right of fixation at study. Trials testing for either associative or source memory were randomly ordered, with no more than three consecutive trials of the same type. Test trials were self-paced and presented as a single block.

4.2.3 EEG/ERP acquisition

Prior to the study phase participants were fitted with an electrode cap, and seated in front of a display monitor in a sound attenuated room. EEG was continuously recorded with a 64-

channel BrainAmp Standard system (www.brainvision.com) using Ag/AgCl sintered ring electrodes embedded in an elastic cap (Easycap, Herrsching, Germany), and sited according to the International 10-20 system. The following sites were recorded from: Fpz/1/2, AFz/3/4/7/8, Fz, F1/2/3/4/5/6/7/8, FC1/2/3/4/5, FT7/8, Cz/1/2/3/4/5/6, T7/8, CPz/1/2/3/4/5/6, TP7/8, Pz/1/2/3/4/5/6/7/8, POz/3/4/7/8, and O1/2 (see Figure 4.2). The data were recorded with reference to an electrode at FCz, and ground electrode at AFz. Additional electrodes were affixed to bilateral mastoid processes, above and below the right eye, and on each outer canthus. The average activity recorded at the mastoids served as an offline-reference, and the activity recorded from the electrodes on the canthi and above/below the right eye was used to measure horizontal and vertical electrooculograms (EOG), respectively. Prior to acquisition, electrode impedances were adjusted to be under 5 kΩ. Impedance was checked and re-adjusted as necessary during rest and break periods. Data were acquired using a 500 Hz sampling rate and a .016-1000Hz (-3 dB points) amplifier bandwidth, with an online software filter bandwidth of .01-70 Hz.

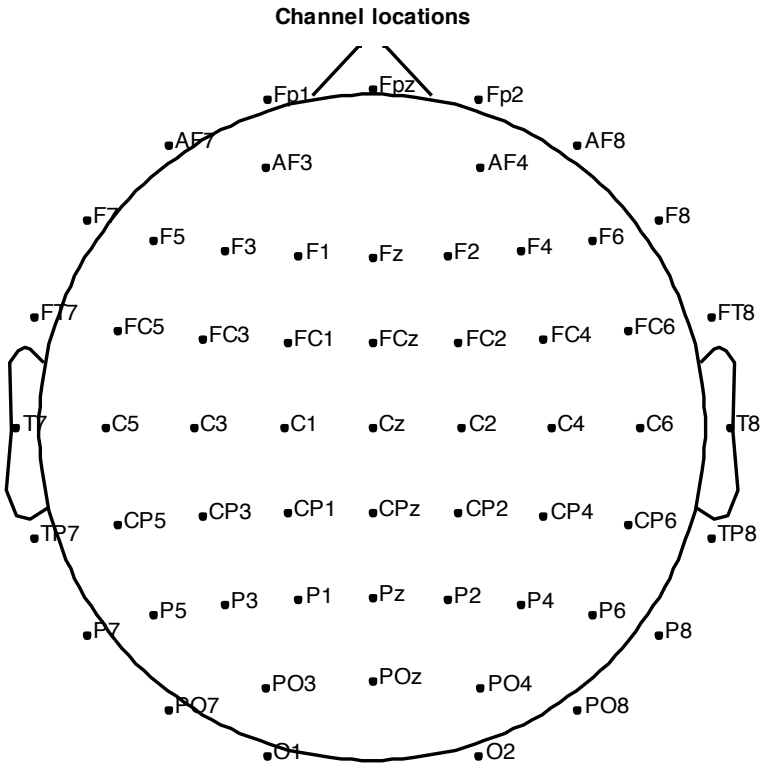

Figure 4.2. Map of the electrode locations on the scalp.

4.2.4 EEG data analysis

To estimate subsequent memory effects for item-item and item-context memory, ERPs at encoding were averaged according to subsequent memory performance: items subsequently recognized and attracting a correct associative judgment (associative correct), items subsequently recognized and attracting an incorrect or DK associative judgment (associative incorrect/DK), and the analogous conditions for correct and incorrect source judgments (source correct and source incorrect/DK). This was done by timelocking the EEG to the onset of the first study item in each trial (the picture). Offline pre-processing of the EEG data was implemented with the EEGLAB toolbox (Delorme and Makeig, 2004) in MATLAB. The continuous data were digitally filtered with a low-pass half-amplitude cutoff of 30 Hz (-3dB at 19.4 Hz), a roll-off of 12 dB/octave, and a Butterworth filter type. Other than the high-pass cutoff applied during data collection, there was no additional high-pass filtering was performed. Data were then re-referenced to the average activity recorded at the mastoids and epoched (-200 to +3500 ms relative to picture onset, Figure 4.4). Mean amplitudes were computed relative to the mean of a 200 ms pre-stimulus baseline period (prior to either the picture or word onset; see Analysis, below).

Independent components analysis (ICA) was used to identify data attributable to ocular artifacts (e.g., horizontal eye movements, blinks, and other vertical eye movements). These components were manually rejected on the basis of scalp topography and power spectra (Jung et al., 2000; see Figure 4.3 for examples). Epochs were also rejected if there was a simple voltage change of ±100 μV, if they contained baseline shift artifacts (±80 μV), and/or any other abnormal activity (e.g., muscle activity) based on a final visual inspection.

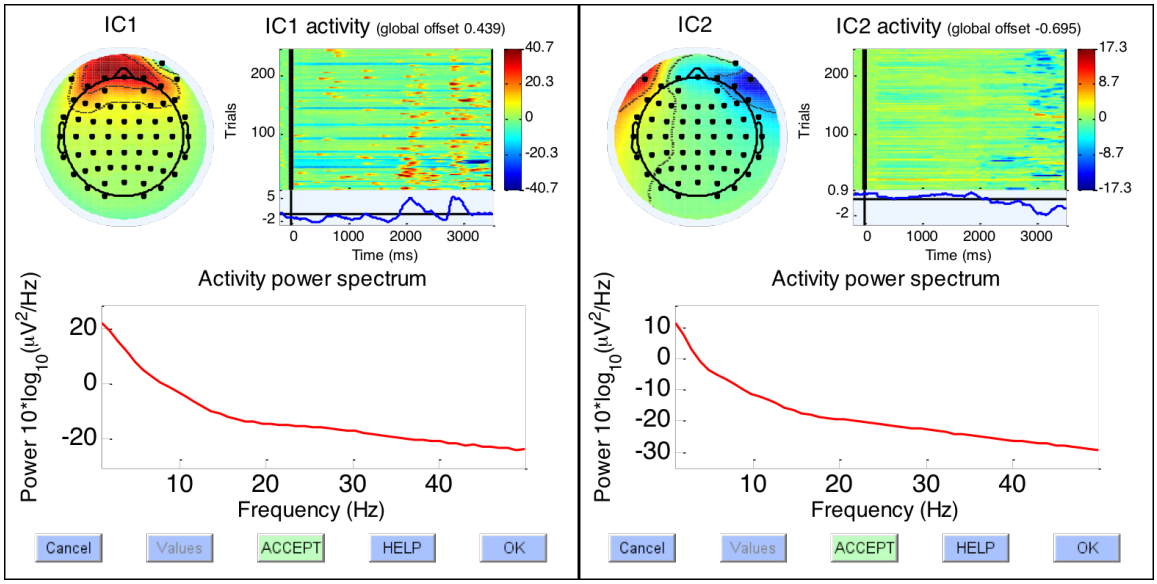

Figure 4.3. Representative ICA components corresponding to ocular artifacts. The left panel shows the scalp topography and power spectrum for a typical blink component. The right panel shows the same for a typical horizontal eye movement.

4.2.4.1 ERP analysis

Analysis of the ERP data was conducted in several stages, using the EEGLAB and ERPLAB toolboxes (Delorme and Makeig, 2004; Lopez-Calderon and Luck, 2014). Epoched data were binned and averaged according to subsequent memory status: associative correct, associative incorrect, source correct, source incorrect, item miss. To maintain an acceptable signal-to-noise ratio, participants' data were excluded based on a minimum criterion of <12 trials per bin, after artifact rejection.

Mean ERP amplitudes were taken from ten 300 ms latency windows spanning the duration of each study trial, starting at picture onset and ending at 3000 ms post-picture onset (0-300 ms, 300-600 ms, 600-900 ms, 900-1200 ms, 1200-1500 ms, 1500-1800 ms, 1800-2100 ms, 2100-2400 ms, 2400-2700 ms, and 2700-3000 ms). For the purpose of addressing our study predictions, these time windows were also delineated according to each of the two stimulus onsets; specifically, latency windows spanning 0-1500 ms comprised the "post-picture" time period, whereas latency windows spanning 1500-3000 ms comprised the "post-word" time period (Figure 4.4). We sought to identify magnitude differences in both the post-picture and

post-word time periods, as well as within the inter-stimulus interval. To identify significant ERP effects elicited by the first stimulus, ERPs were measured with respect to the mean of the 200 ms interval prior to the picture stimulus; this identified effects that were present in the picture stimulus period and potentially sustained into the word stimulus period. Significant ERP effects elicited by the second stimulus were identified by measuring ERPs respect to the mean of the 200 ms interval prior to the word stimulus. After discovering that the onset of effects in the post-picture epoch was too early to be elicited by the picture, we investigated effects that onset prior to the picture. In this "prestimulus" time period, ERPs were measured with respect to the mean of the 200 ms interval prior to the onset of the red cross, allowing pre-stimulus effects from -600 to 0 ms to be examined (Figure 4.4).

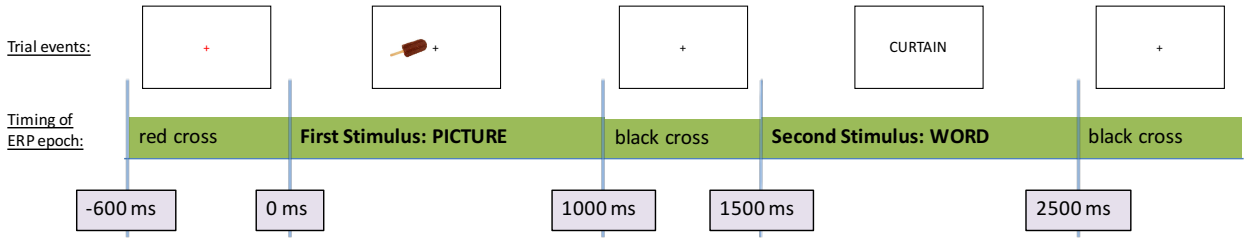

Figure 4.4. Schematic of the events within an EEG-recorded study trial (top row), with corresponding timing (bottom row).

4.2.4.1.1 Mean amplitude analyses: 42 electrodes

For the main set of analyses, data from 42 electrode sites (Figure 4.5) were used for statistical evaluation. This resulted in equal factorization according to the breakdown listed below. Repeated-measures ANOVAs were initially conducted in each 300 ms latency window, in order to determine whether there were any memory effects that differed as a function of task. The repeated measures factors were: task (associative, source), subsequent memory (correct, incorrect/DK), hemisphere (left, right), the anterior-posterior dimension (which had seven levels corresponding to each row of electrodes; see Figure 4.5), and site (three electrode positions within each half of each row, spanning mid-lateral; Figure 4.5). Then, follow-up ANOVAs were

conducted separately for each task, in order to determine whether there were reliable subsequent memory effects for each task. Mean numbers of trials (ranges in parentheses) contributing to remembered and forgotten judgments in the associative task were 58 (28-91) and 23 (13-43). The corresponding mean trial numbers for the source task were 55 (25-81) and 30 (12-52).

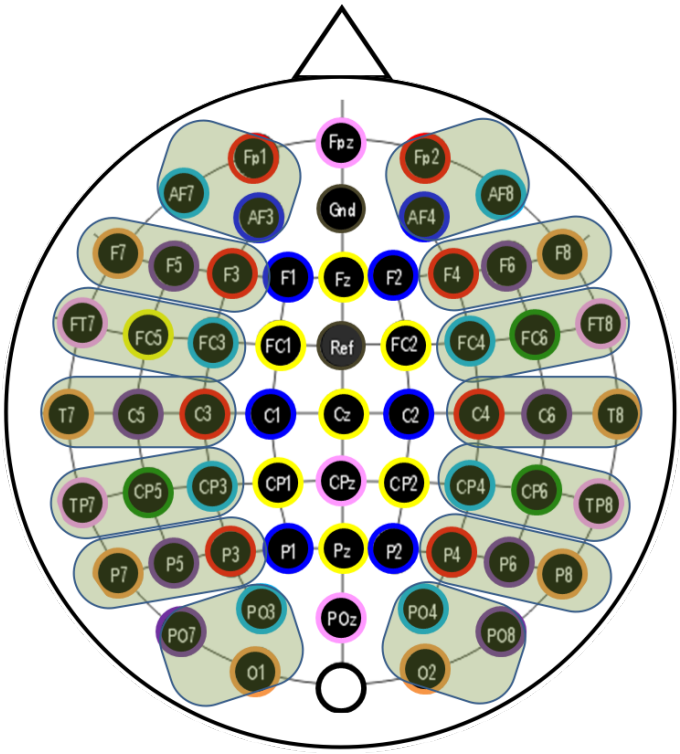

Figure 4.5. Map of electrodes used for statistical evaluation.

4.3 Results

4.3.1 Behavioral performance

4.3.1.1 Study task

Mean accuracy on the study task was 0.77 (SD = 0.09). Study RTs are shown in Table 4.1. segregated according to later memory performance. A one-way ANOVA revealed no significant differences in RT between the four subsequent memory conditions ($F < 1$).

Table 4.1. Mean reaction times (ms) for correct size/hand judgments at study segregated by subsequent memory (SD in parentheses).

Subsequent Memory Judgment	Reaction Time (ms)
Associative Correct	1583 (358)
Associative Incorrect/DK	1593 (410)
Source Correct	1585 (390)
Source Incorrect/DK	1589 (382)

4.3.1.2 Retrieval task

The item hit rate was 0.70 (SD = 0.13) against a false alarm rate of 0.12. Conditionalized on accurate item recognition, the proportions of accurate associative and source judgments were 0.69 (SD=0.11) and 0.65 (SD=0.11) respectively. Following prior studies (e.g. Gottlieb et al., 2012, Wong et al., 2013; c.f. Chapter 3), associative and source memory were estimated with an index derived from a single high-threshold model, in which the probability of recollection was computed as p(recollection) = {p(Hits) – 0.5[1 – p(DK)]} / {1 – 0.5[1 – p(DK)]}. The index was calculated separately for associative and source memory. Associative and source memory estimates were 0.45 (SD = 0.17) and 0.38 (SD = 0.16), respectively. Pairwise contrasts revealed that both performance estimates were significantly greater than the chance value of zero ($t(24) = 11.80$, $p < 0.001$, and $t(24) = 13.16$, $p < 0.001$ for associative and source judgments, respectively), and that associative memory accuracy was not significantly different from the source memory accuracy. The correlation between performance on the two memory tests was not significant ($r = 0.21$, $p = 0.32$).

4.3.2 Subsequent memory ERP analyses

To address our study predictions, the group averaged ERP waveforms for each study condition were separately timelocked to the picture and the word. Upon visual inspection of the waveforms timelocked to the picture (Figure 4.6), we noticed that the source correct and

incorrect/DK waveforms were already diverging at 0 ms, which led us to suspect that there was a memory effect that occurred prior to picture onset.

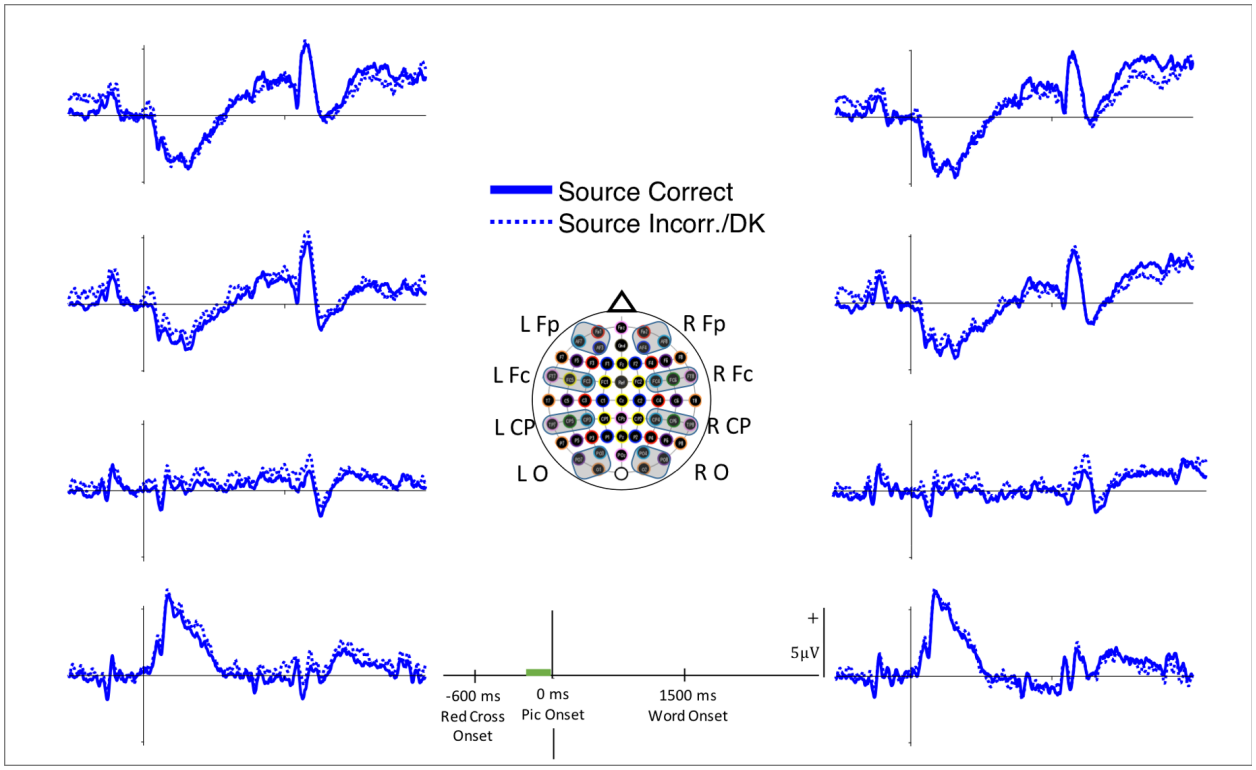

Figure 4.6. Representative ERP waveforms for the source correct and source incorrect/DK conditions, baselined to the 200 ms interval preceding picture onset (green shaded region on time axis).

As alluded to in the ERP Analysis section, we followed up on this observation by timelocking ERPs to the red cross stimulus that preceded the picture, both separately for the associative (Figure 4.7) and source waveforms (Figure 4.8), as well as for ERPs collapsed across task (Figure 4.9). These ERPs were measured with respect to the mean of the 200 ms interval preceding red cross onset. Upon visual inspection of these ERP waveforms, we identified what looked to be a prestimulus effect, that was sustained as a positive-going memory effect throughout most of the trial. Since timelocking to the picture had resulted in ERP waveforms that obscured this latter effect (Figure 4.6), subsequent statistical analyses were only carried forward with ERP waveforms baselined on the 200 ms preceding red cross onset.

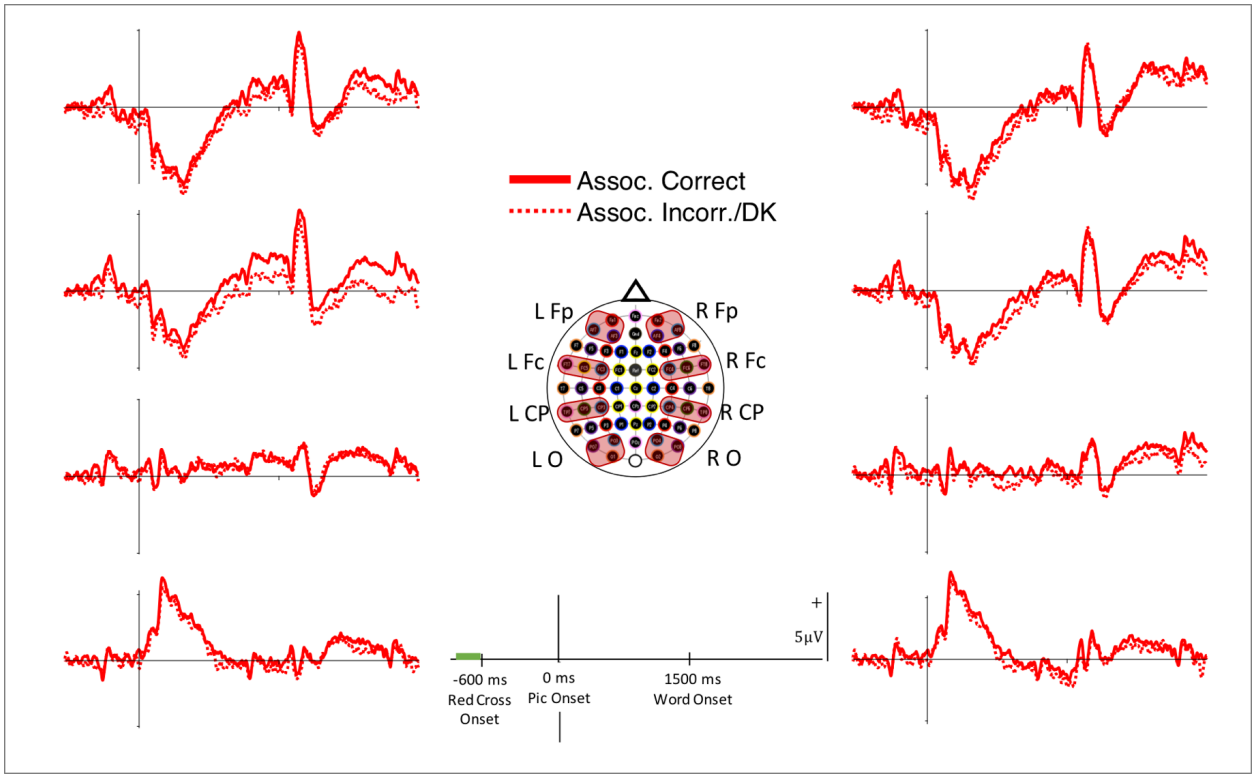

Figure 4.7. Representative ERP waveforms for the associative correct and associative incorrect/DK conditions, baselined to the 200 ms interval preceding red cross onset (indicated by the green shaded region on the time axis).

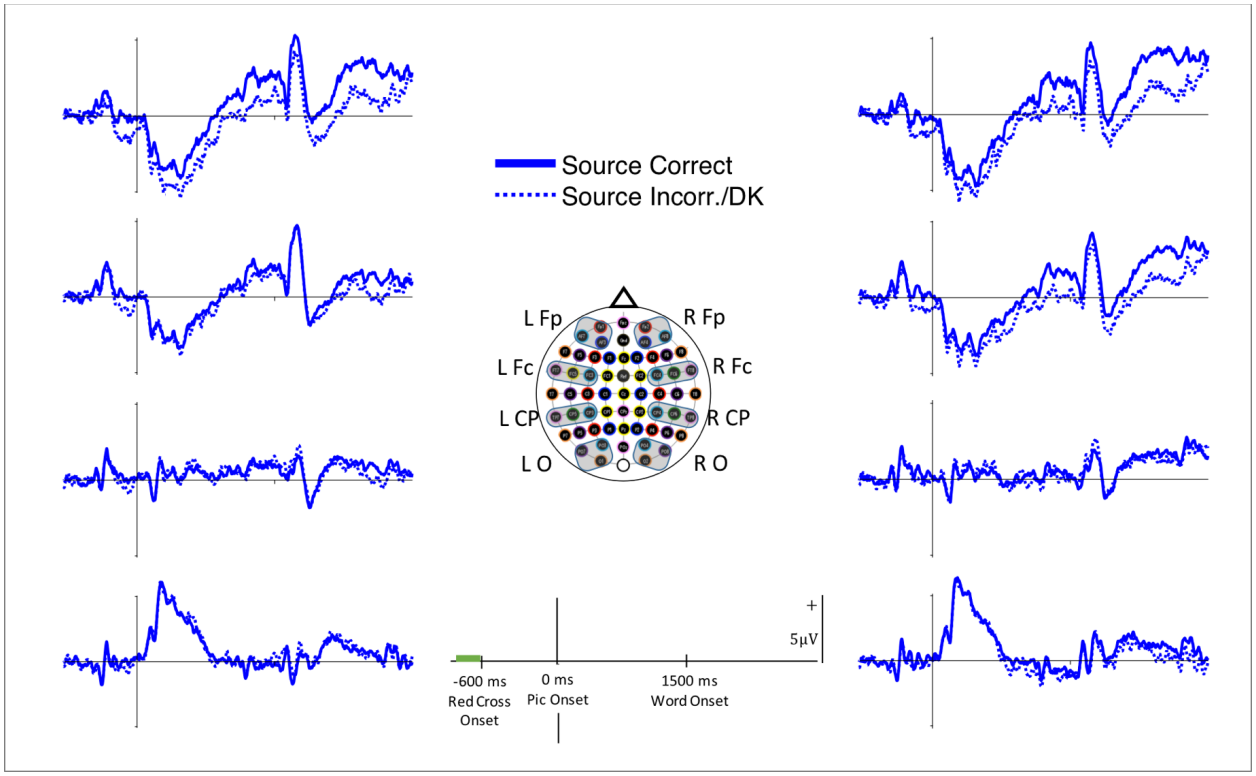

Figure 4.8. Representative ERP waveforms for the source correct and source incorrect/DK conditions, baselined to the 200 ms interval preceding red cross onset (indicated by the green shaded region on the time axis).

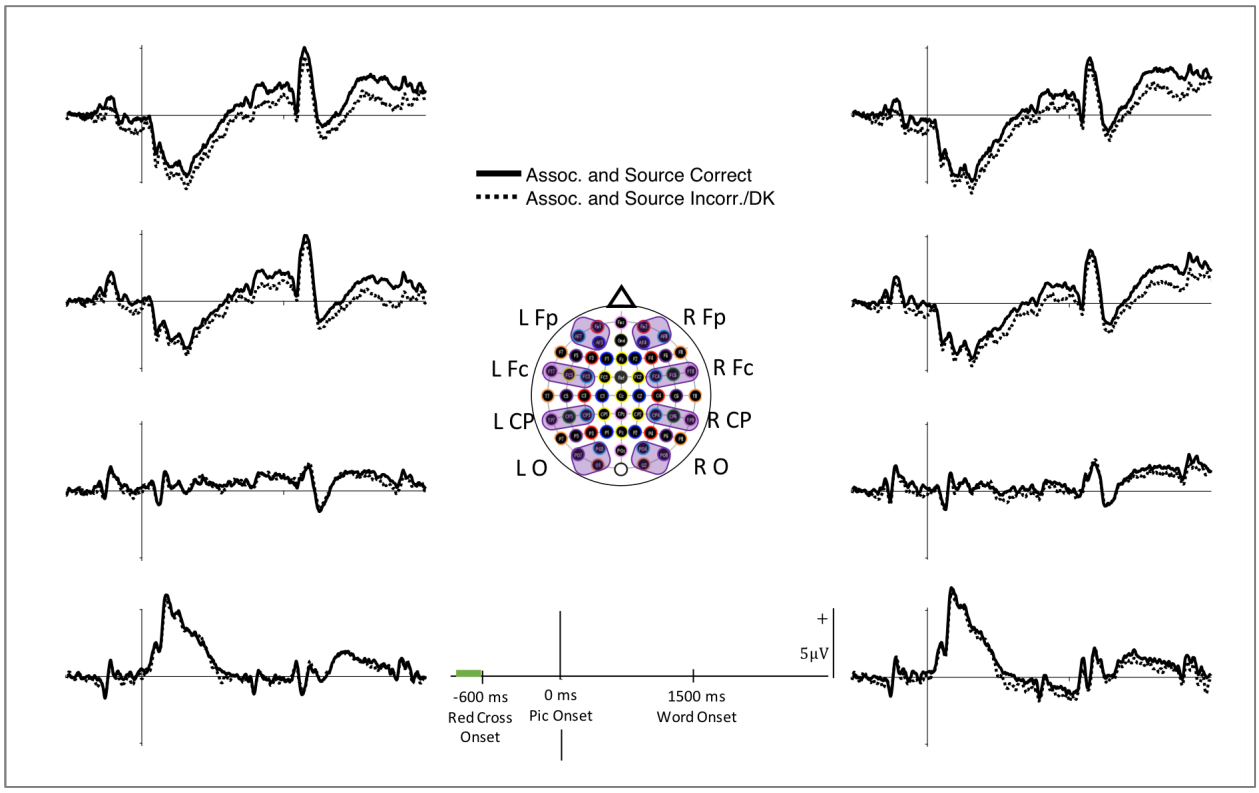

Figure 4.9. Representative ERP waveforms for the associative/source correct and associative/source incorrect/DK conditions, baselined to the 200 ms interval preceding red cross onset (indicated by the green shaded region on the time axis).

Repeated-measures ANOVAs were initially conducted within consecutive 300 ms latency windows (factors of task, subsequent memory, site, anterior/posterior, hemisphere). There was a main effect of memory in the -300-0, 900-1200, 2100-2400, and 2700-3000 ms time windows (Table 4.2). As suggested by the voltage distribution of the memory effects in these time windows (Figure 4.10), the common subsequent memory effects were in the form of more positive-going ERPs for remembered information, particularly in bilateral fronto-polar electrode sites. Subsequent memory also interacted with task and other electrode factors in the 0-300, 1200-1500, 1500-1800, and 2400-2700 ms time windows. For these time windows in which a subsequent memory by task interaction was found, follow-up ANOVAs were conducted separately for each task. These analyses revealed reliable subsequent memory effects for source only (Table 4.3).

Table 4.2. ANOVA table for across-task mean amplitude analyses.

ACROSS-TASK	PRE-STIM	PICTURE EPOCH			WORD EPOCH			
	-300-0 ms	0-300 ms	900-1200 ms	1200 – 1500 ms	1500 – 1800 ms	2100 – 2400 ms	2400 – 2700 ms	2700 – 3000 ms
MEM	F(1,20) = 9.698, p = .005		F(1,20) = 6.73, p = .017	F(1,20) = 7.239, p = .014		F(1,20) = 6.071, p = .023	F(1,20) = 11.106, p = .003	F(1,20) = 7.331, p = .014
MEM * TASK * HEMI				F(1,20) = 5.893, p = .025	F(1,20) = 5.027, p = .036		F(1,20) = 5.497, p = .029	
MEM * TASK * HEMI * AP		F(2.876, 57.51) = 2.952, p = .042						
Note: MEM = memory; HEMI = hemisphere; AP = anterior/posterior								

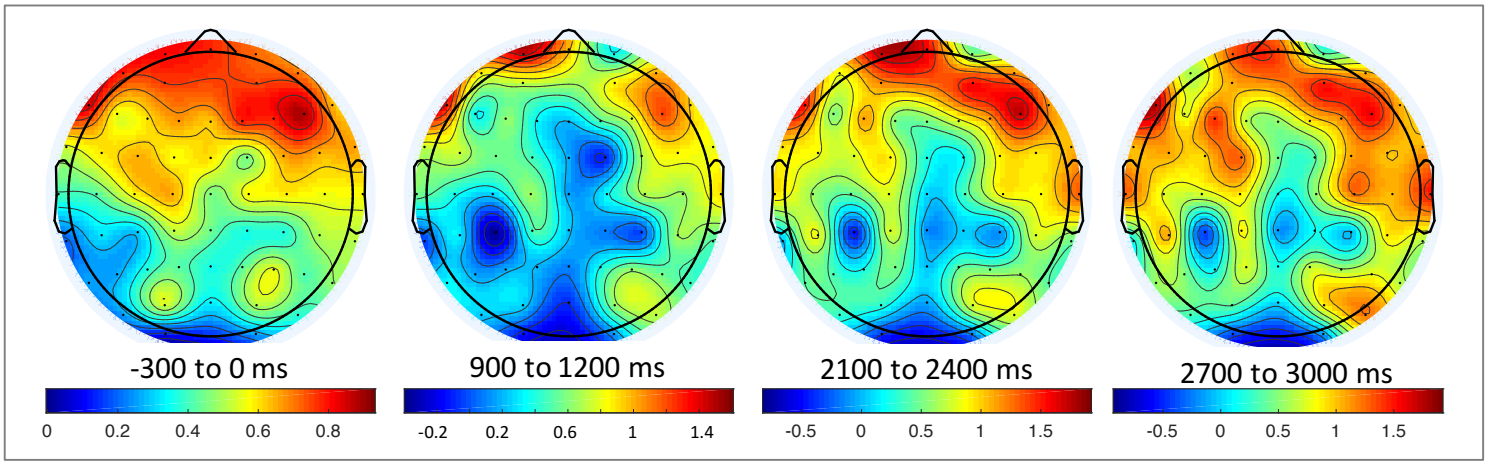

Figure 4.10. Topographic maps show distribution of common subsequent memory effects (associative and source correct minus associative and source incorrect/DK) across the scalp, scaled to the minimum (blue) and maximum (red) values within each time window. The time windows displayed are those in which a main effect of memory was found in the across-task ANOVA.

Table 4.3. ANOVA table for within-task mean amplitude analyses.

WITHIN-TASK: SOURCE	PICTURE EPOCH	WORD EPOCH	
	1200 – 1500 ms	1500 – 1800 ms	2400 – 2700 ms
MEM	F(1,20) = 8.615, p = .008		F(1,20) = 9.219, p = .007
MEM * HEMI	F(1,20) = 7.896, p = .011	F(1,20) = 5.504, p = .029	
MEM * AP		F(2.245, 44.899) = 3.575, p = .032	F(1,20) = 4.336, p = .02
MEM * SITE	F(1.243, 24.856) = 4.015, p = .048		
Note: MEM = memory; HEMI = hemisphere; AP = anterior/posterior			

4.3.3. Topographic analyses

Topographic analyses were conducted to compare the scalp distributions of associative and source subsequent memory effects, within the latency windows in which task by subsequent memory interaction effects were identified in the previous section. If the scalp distributions were statistically different, it would suggest that the associative and source subsequent memory effects in these time windows were the outcome of dissociable intra-cerebral generators. An ANOVA of memory difference scores was conducted (i.e., associative correct > associative incorrect and source correct > source incorrect), with the same factorization of electrode factors described above (i.e., hemisphere, anterior/posterior, site). Difference scores were range-normalized prior to analysis to remove the confounding effects of overall differences in effect magnitude (McCarthy and Wood, 1985; Wilding, 2006). The ANOVAs revealed a significant interaction between task and hemisphere in the 1200-1500 ms ($F(1,20) = 4.809$, $p<0.05$), and 2400-2700 ms ($F(1,20) = 5.499$, $p<0.05$) time windows. As illustrated in the topographic maps (Figure 4.11) and ERP waveforms (Figure 4.12) shown below, this task by memory by hemisphere interaction was in the form of greater associative than source subsequent memory effects in left hemisphere

electrode sites, and greater source than associative subsequent memory effects in right hemisphere electrode sites.

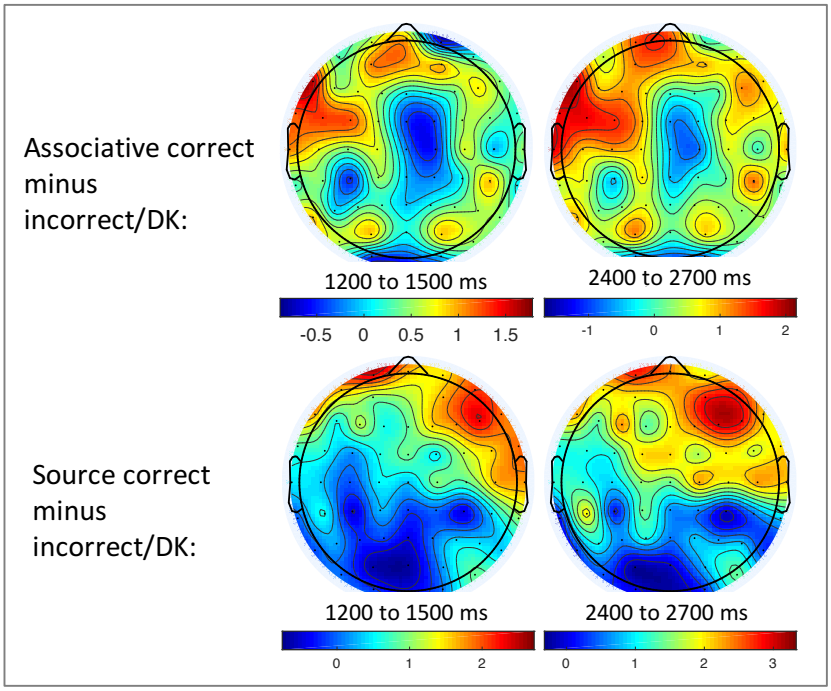

Figure 4.11. Topographic maps showing the distribution of associative (top row) and source (bottom row) subsequent memory effects across the scalp in two latency regions. The maps are scaled to the respective minimum and maximum voltage in each task condition and latency window.

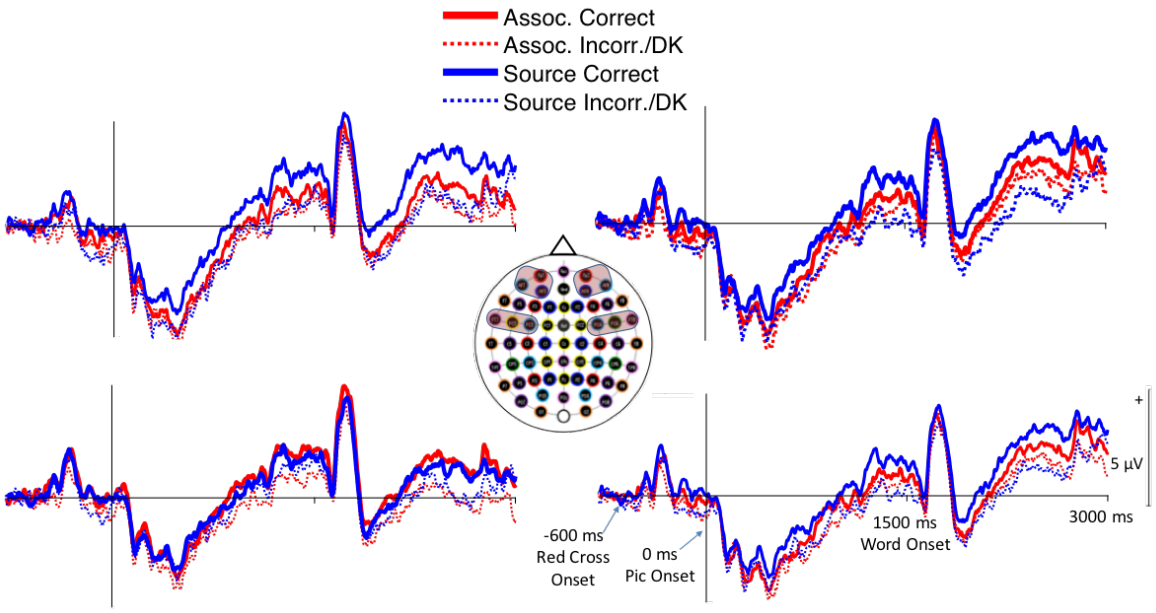

Figure 4.12. ERP waveforms displaying a task by subsequent memory by hemisphere interaction (c.f. Figure 4.11).

4.4 Discussion

4.4.1 Behavioral findings

There were no significant RT differences between study trials according to performance on the later memory test, making it unlikely that differences in EEG/ERP subsequent memory effects reflected differences in the efficiency with which the study events were processed. Unlike the fMRI version of this experiment, source memory performance was not more accurate than that of associative memory. This could be because the experimental procedure was modified from the fMRI version to ensure equal performance rates between the two tasks (see Methods). Finally, the correlation between associative and source memory performance was non-significant, which is consistent with the fMRI findings, and suggests that the processes supporting the encoding of associative and source information were at least partially independent.

4.4.2 Subsequent memory ERP findings

When using an early prestimulus baseline, ERP subsequent memory effects onset prior to the first study item, were both common and task-specific to associative and source memory, and were in the form of a sustained positivity throughout the entire epoch. These results suggest that the effective encoding of both associative and source information was dependent on neural activity elicited prior to the event itself (i.e., the picture), which supports prior findings that anticipatory (prestimulus) processes may play a role in memory formation (Otten et al., 2006).

4.4.3 Topographic analysis findings

When investigating the task by memory interaction effects identified in the mean amplitude analyses, we found that the scalp distributions of the associative and source subsequent memory effects were statistically different in the 1200-1500 ms and 2400-2700 ms time windows, which suggests that these effects originated from neurally distinct activity and possibly distinct neural generators. In particular, the task by hemisphere interaction of the subsequent memory effects was in the form of a greater associative subsequent memory effect than source subsequent memory effect in left hemisphere, and the reverse pattern (greater source than associative) in right hemisphere. One possible interpretation that immediately comes to mind is that the lateralization of associative and source ERP effects reflect the lateralization of fMRI subsequent memory effects found in the fMRI version of this study (Wong et al., 2013; Chapter 3), which identified left lateralized associative subsequent memory effects and a right lateralized source subsequent memory effect. However, although it is tempting to relate the task-dissociable ERP effects to the fMRI effects just mentioned, we cannot rule out the possibility that the ERP effects are more closely tied to the common negative subsequent memory effect we identified as well in the precuneus (Chapter 3, Figure 3.2).

4.4.4 General conclusions

The goal of this study was to investigate the ERP correlates of encoding item-item (associative) and item-context (source) information. Only one of our three initial predictions was supported by the findings; namely, the scalp distributions of the ERP subsequent memory effects

were found to differ across tasks, which we had predicted based upon the task-dissociable subsequent memory effects identified in the fMRI version of this study. With regard to the other two predictions: 1) A polarity reversal of subsequent memory effects was not found, as all ERP memory effects were more positive-going, and 2) There was no dissociation in when ERP subsequent memory effects appeared within each study trial, as all ERP memory effects were found throughout the trial.

Although our findings do not correspond with those of previous studies which reported polarity differences in subsequent memory effects across different types of encoded information (e.g., Bridger and Wilding, 2010; Otten and Rugg, 2001), we cannot rule out the possibility that the distinction between the encoding of conceptual versus perceptual information was not manifested in a different way in our pattern of ERP findings. That is, although we did not observe positive-going ERP modulations for subsequently remembered associative information, and negative-going ERP modulations for subsequently remembered source information, we argue that our findings dissociate between these categories in the form of left-lateralized effects for associative, and right-lateralized effects for source. Furthermore, our findings do not necessarily depart from the positive-negative polarity distinction found for processing conceptual-perceptual information. For instance, we cannot rule out the possibility that the positive-modulation for all of our ERP memory effects reflects the incorporation of both associative and source information into a primarily conceptual, semantic-based representation, one which is putatively indexed by positive-going ERP modulations.

We found that both common and task-specific ERP subsequent memory effects were distributed throughout the entire trial. In particular, all of these memory effects seem to have been elicited by the presentation of the red cross, which we alluded to earlier as reflecting the role of anticipatory processes playing an important role in memory formation for subsequently presented task-relevant information. The presence of both associative and source subsequent memory effects throughout the entire trial epoch may also reflect the interplay between processing associative and source information that is necessary for participants to successfully perform a “Which is smaller?” judgment. Namely, attention to source information was required as soon as participants saw the first stimulus (picture) and its location, and had to be sustained

until the end of the trial in order for participants to respond with the correctly lateralized hand. Analogously, attention to associative information was also required at the first stimulus and had to be sustained until the end, since participants needed to process semantic properties of the first and second stimuli (picture and word) in order to make their response. The presence of task-specific effects in the form of a hemispheric dissociation may have occurred at times when it was important to dedicate left and right hemisphere-based neural generators to processing associative and source-specific information, respectively.

CHAPTER 5

GENERAL DISCUSSION AND CONCLUSIONS

5.1 Summary of results and interpretations

The motivation behind the three experiments described in Chapters 2-4 was to identify the neural correlates of encoding episodic memory associations. Experiment 1 directly contrasted the neural correlates of encoding information that supports later judgments of temporal order with those that support the encoding of item-item associations. Whereas the encoding of item-item associations was found to involve greater activation in the LIFG, as was characteristically found in prior studies (Chapter 1), this region was not found to be involved in the successful encoding of the temporal order of an item relative to its pairmate. Rather, the successful encoding of temporal order information was associated with subsequent memory effects in the bilateral fusiform and occipital cortex, which suggests that the encoding of temporal order information between two items involves processes independent from those important for encoding item-item associations. The behavioral findings support this interpretation in that temporal order memory performance was found to be more accurate and not correlated with associative memory performance. Thus, participants were better able to remember an item's temporal order position relative to the other item, even when unable to recall the identity of the other item. Taken together, these findings suggest that the encoding of temporal order information may be more akin to the encoding of item-context rather than item-item associations.

Experiment 2 directly contrasted the neural correlates of encoding item-item and item-context associations. Here again, the LIFG was found to support the encoding of item-item associations selectively—item-context associations were supported by greater activity in the right fusiform cortex. Behaviorally, item-context memory performance was better than item-item memory, and performance on the two tasks was uncorrelated. This dissociation in the patterns of neural correlates further supports the interpretation that the encoding of item-item and item-context associations involves qualitatively different neural processes. Specifically, the dissociation in the subsequent memory effects we identified were thought to correspond to a

dissociation in the set of regions that were especially important for processing item-item and item-context information in a way that would lead to later successful memory for that information.

Finally, the experiment proposed and conducted for the dissertation (Experiment 3) was motivated by the aim of characterizing the temporal correlates of encoding item-item and item-context associations. Using the same study design as in Experiment 2, slightly modified for EEG, we identified and contrasted ERP correlates of successful memory encoding for item-item and item-context information. The findings addressed three main predictions regarding the temporal and qualitative nature of these ERP effects. First, based upon findings from the fMRI version of this study (Experiment 2), we predicted that the encoding of associative and source information would elicit qualitatively different scalp distributions of subsequent memory effects, reflecting different patterns of neural activity in the brain. We also cautiously proposed that the regions showing subsequent memory effects in the fMRI study would serve as potential candidates for the neural generators of subsequent memory effects in the EEG domain. Although there is not a one-to-one mapping between the subsequent memory effects identified via fMRI and ERP, the presence of an associative subsequent memory effect in left frontal electrode sites seems to correspond with the LIFG associative subsequent memory effect identified in the fMRI study. As discussed in Experiment 3, the prediction regarding the scalp distribution was the only one of the three predictions that was supported by our findings. Namely, a hemispheric dissociation was found between associative and source memory effects throughout the picture and word epochs.

Our second prediction was based upon the subsequent memory ERP studies reviewed in Chapter 1, namely that there would be a dissociation in the polarity of the ERP subsequent memory effects, with correctly remembered associative information eliciting more positive-going ERP effects, and correctly remembered source information eliciting more negative-going ERP effects. This pattern of voltage reversal was not found in our study, as all of our ERP memory effects were more positive-going. Finally, our third prediction was that there would be a dissociation in when ERP subsequent memory effects appeared during each trial, in that source SMEs would arise soon after the onset of the picture and its location, and that associative SMEs would also onset at picture presentation and be sustained until word presentation. Specifically,

we expected source subsequent memory effects to arise as soon as the source information was available (in this case, when the picture was presented on either the left or right side of the screen). Associative subsequent memory effects were anticipated sometime after the picture has been presented, since the successful formation of an item-item association between the picture and the subsequently presented word would presumably require successful encoding of the picture itself. As described in Experiment 3, this pattern was not observed, as ERP memory effects were found throughout the entire trial period, starting in the prestimulus epoch.

5.2 General discussion

In the three experiments included in this dissertation (Chapters 2-4), we investigated the neural correlates of successfully encoding episodic memory associations. Specifically, by contrasting neural activity elicited by study of items that were subsequently remembered vs. activity for study items that were subsequently forgotten, we were able to identify subsequent memory effects that indexed encoding operations that led to later successful memory for item-item, item-context, and temporal order information. Although each type of memory association had been investigated on its own in previous studies, the three experiments in this dissertation were the first to directly compare their subsequent memory effects in common experiments. Each study design had two critical features: 1) participants encoded two types of memory associations incidentally, to minimize the likelihood that they would adopt strategies for later remembering each type of information, and that 2) participants performed the same encoding task for every trial, such that any subsequent memory differences between trials later remembered for one vs. the other type of memory association would be from differences in the initial processing of each type of memory association. Having controlled for these factors, we found that successful memory for different types of memory associations was mediated by qualitatively different patterns of neural correlates (as was summarized in the previous section).

A key goal that was common across the three studies was to elucidate the nature of item-item associations. The neural correlates of encoding item-item information were directly compared to those of encoding temporal order (Experiment 1) and item-context associations (Experiment 2). Prior to these studies, it was still an unanswered question as to whether there were neural correlates that were common to the encoding of all types of associative information,

regardless of the content. For instance, fMRI studies of associative memory had consistently identified the LIFG as a region that showed greater activation for processing associations that were later remembered vs. forgotten (Chapter 1). In fact, subsequent memory effects in this region were not unique to the encoding of memory associations, as they had also been reported for the encoding of individual items since the inception of the subsequent memory procedure in fMRI studies (Wagner et al., 1998). The LIFG has a well-established role in supporting the controlled retrieval and selection of task-appropriate item representations (Chapter 1). We conjectured that it is this role of the LIFG that supports the formation of well-specified item representations, which in turn facilitate the successful encoding of item-item associations. Furthermore, one of the main achievements of the first two studies we conducted was to specify the role of the LIFG in item-item encoding, separate from the regions supporting the temporal order association between two items (Experiment 1), and those supporting the associations between an item and its spatial context (Experiment 2).

One important future direction to take in light of the findings from Experiment 1 would be to conduct a study that directly compared the encoding of temporal order and item-context associations. As summarized in the preceding section, these findings suggested that temporal order information is not encoded via the formation of inter-item associations. Rather, temporal order information may be encoded by the formation of associations between items and their temporal context, as proposed by earlier computational models (Estes, 1955; Bower, 1972; Mensink and Raaijmakers, 1989; Howard and Kahana, 2002). Evidence supporting a temporal context model has also been found in more recent fMRI studies which have demonstrated that memory for temporal sequences was sensitive to shifts in study context (Tubridy and Davachi, 2011; Dubrow and Davachi, 2014), which in turn may be supported by changes in hippocampal activity patterns over time (Jenkins and Ranganath, 2016; for the most up-to-date review, see Ranganath and Hsieh, 2016). The predicted pattern of results from a study that directly compared temporal order and source encoding are less clear cut than what we might expect (and have found) in a comparison of temporal order and associative encoding. Namely, whereas studies of associative encoding have consistently identified enhanced activity in the LIFG, there does not seem to be an analogously ubiquitous region associated with subsequent memory for

source/item-context information (with the exception of the hippocampus and possibly surrounding regions of the MTL). Rather, it would seem that the encoding of item-context information, relative to item-item encoding, is more heavily dictated by the nature of the encoded information; whereas LIFG activity has been identified across various classes of "items" involved in item-item encoding, variations in the nature of the "contexts" involved in item-context encoding (e.g., sensory modality, color, location; see Chapter 1) have, with the exception of the hippocampus/MTL, generally yielded cortical subsequent memory effects specific to regions thought to be involved in the online processing of the contextual feature itself. Interestingly, a further complication of this proposed study is that if the encoding of an item's temporal order is dependent on associations between the item and its "temporal context," it is possible that an experimental manipulation of a contextual feature (e.g., color, location) across trials would influence the encoding of not only the contextual feature associated with the item, but also the encoding of the item's temporal order. Given this possibility, it is especially important to design an experiment that asks whether temporal order encoding and item-context encoding involve qualitatively different neural correlates, and thus potentially functionally independent processes. As there has only recently been sustained interest in investigating the fMRI correlates of temporal order encoding, it is unclear whether the subsequent memory effects we identified for order memory in Experiment 1 comprised regions selectively involved in processing an item's order information independently from all other types of associations. In fact, in our discussion of Experiment 1, we had speculated about the involvement of the right fusiform cortex in temporal order encoding, since source subsequent memory effects have also been identified in this region in prior studies (e.g. Cansino et al., 2002; Ranganath et al., 2004; Sommer et al., 2005; Uncapher and Rugg, 2009), and in our own investigation of item-context encoding in Experiment 2. As was discussed in Gottlieb et al. (2012), where we identified conjoint location and voice subsequent memory effects in the right lateral occipital cortex, it may be the case that subsequent memory effects in a brain region strongly implicated in object processing reflect the allocation of a relatively large amount of attentional resources to an item, facilitating its perceptual processing. Given the variation in the precise location of right fusiform subsequent memory effects across the temporal order and item-context studies we have just

cited, we cautiously propose that the right fusiform cortex would demonstrate enhanced activity for the successful encoding of both an item's temporal order and whichever associated source feature we choose to vary across trials.

Another future direction would be to follow-up the ERP analyses currently being reported in Experiment 3, by performing a frequency decomposition of the EEG data to investigate the neural oscillations underlying the encoding of associative and source information.[9] Neural oscillations reflect rhythmic fluctuations in the excitability of neurons or populations of neurons (Buzsaki, 2006; Cohen, 2014), and brain oscillatory correlates of memory formation have been identified in a wide range of frequency bands, ranging from delta (~2-4Hz) to theta (~4-8 Hz) to alpha (~8-12 Hz) to beta and gamma (~20-80 Hz), and simple parameters (e.g., power or coherence; Hanslmayr and Staudigl, 2014). Positive subsequent memory effects (in this context, increases in power for subsequently remembered items) have mainly been found in the theta and gamma frequency ranges (see Duzel et al., 2010; Nyhus and Curran, 2010, for reviews), whereas negative subsequent memory effects (i.e., decreases in power for subsequently remembered items) have been reported in the alpha and beta frequency range (e.g., Hanslmayr et al., 2009). The authors concluded that this qualitative distinction between the subsequent memory effects may reflect the difference in how information was initially processed during encoding. In this case, it was found that alpha and beta power decreases were specifically related to semantic encoding, and theta power increases were specifically related to non-semantic encoding. This finding is particularly relevant to the predictions one might make based upon the putative semantic vs. non-semantic distinction we found in our own pattern of ERP results (i.e., positive-going ERPs for encoding associative information, and negative-going ERPs for encoding source information).

5.3 Conclusions

In the series of experiments presented in this dissertation (Chapters 2-4), we were able to identify subsequent memory effects that indexed encoding operations that led to later successful memory for item-item, item-context, and temporal order information. In line with previous fMRI

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[9] This analysis was included in the dissertation proposal, but left out of the current dissertation document due to time constraints.

studies, we found that the loci of subsequent memory effects localized to regions involved in the online processing of an event. We advanced our understanding of how successful episodic encoding takes place when we must simultaneously pay attention to the multiple features associated with an item (i.e., another item, its location, its temporal order) in order to perform an incidental encoding task. Evidence was found to contest the hypothesis that the LIFG might be equally involved in encoding all types of information associated with an item, taking on a role akin to that of the hippocampus in binding together representations of the different aspects of an experience. By directly contrasting two different types of associations in our first two (fMRI) experiments, we demonstrated that the LIFG is preferentially involved in the successful encoding of item-item associations, over item-context and temporal order associations. Since the fMRI correlates of encoding-related processes only provide a partial picture of the actual neural correlates of encoding-related processes, we continued our investigation of the ERP correlates associated with encoding item-item and item-context information in the experiment specifically proposed for this dissertation (Experiment 3). It was shown that the successful encoding of associative and source information involved neurally dissociable ERP correlates, in the form of different patterns of scalp distributions thought to index the distinction between the semantic and non-semantic/perceptual nature of the encoded associative and source information, respectively. Given that there are different preconditions for detecting task- and/or stimulus-evoked changes with EEG and fMRI (e.g., duration of evoked neural activity; Rugg, 1995), it is possible that the ERP and fMRI correlates we identified are indexing somewhat independent aspects of the neural activity responsible for encoding associative and source information. Collectively, the findings across the three experiments converge to form a larger picture of how qualitatively different neural correlates can underlie the processing of different aspects of an experience in a way that gives rise to a subsequent memory for different aspects of that experience.

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VITA

Jenny Wong was born in Brooklyn, New York on June 21, 1988. Her immigrant parents instilled the importance of education from an early age, and nurtured her hobbies of watching her favorite television series, Sesame Street, and frequenting her local library. She was fortunate to have had access to the best academic programs that the NYC public school system had to offer, and eventually enrolled in Boston College as a first-generation college student. While pursuing a bachelor's degree in Psychology, she joined the Cognitive and Affective Neuroscience lab of Dr. Elizabeth Kensinger as an undergraduate research assistant. Her research endeavors in Dr. Kensinger's lab culminated in an undergraduate honors thesis on memory suppression. After a taking a year after college graduation to work as a full-time research assistant, Jenny enrolled in the School of Behavioral and Brain Sciences at UT Dallas as a PhD student in August 2011. Under the faculty mentorship of Dr. Michael Rugg, she focused her graduate research on investigating the neural correlates of encoding memory associations.