The electrophysiological and neuropsychological organization of long term memory

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The Electrophysiological and Neuropsychological Organization of Long Term Memory

By

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The Electrophysiological and Neuropsychological Organization of Long Term Memory

Abstract

The electrophysiological correlates of recognition memory retrieval were examined in order to identify the neural conditions that precede accurate memory retrieval, characterize the processes that contribute to high and low confidence memory responses, and determine which memory processes are impaired after brain injury. Human electroencephalogram (EEG) was recorded during recognition confidence and source memory judgments in three experiments.

In Experiment 1, mid-frontal pre-stimulus theta oscillations were found to precede the stimulus presentation of items that were successfully recollected, but they were not found to be predictive of item familiarity. Moreover, during stimulus presentation, recollection was associated with an increase in theta over left parietal regions, and the magnitude of this effect was predicted by the earlier per-stimulus theta effects. The results suggest that pre-stimulus processes set the stage for and facilitate subsequent recollection.

In experiment 2, high and low confidence source memory judgments were found to be supported by two electrophysiologically distinct processes. Whereas correct high confidence source memory was associated with a late positive component indicative of recollection, correct low confidence source memory was associated with a late onset negative going ERP that was distinct from both recollection and familiarity based responses. The results indicate that correct source memory responses can be observed even in the absence of recollection.
In experiment 3, ERPs were recorded in amnesics in order to determine whether they exhibited selective deficits in recollection, as previous behavioral studies had suggested. Behavioral data showing relatively preserved item recognition along with severely impaired source recollection was consistent with prior studies of these patients, and ERPs revealed that the patients showed no evidence of recollection-related neurophysiology, but maintained normal ERP correlates of familiarity. These results indicate that these patients exhibit selective recollection deficits, are consistent with dual process models of memory, and suggest that source memory depends critically upon the medial temporal lobe structures, such as the hippocampus, which are typically disrupted in amnesia.
Chapter 1: Background & Significance

*How do we consciously remember, why do we forget, and what goes wrong when people have amnesia from different diseases, dementia, or injury?* These are questions that have plagued researchers and philosophers alike, from Aristotle to St. Augustine (Aristotle, Ross, & Smith, 1910; Augustine & Pusey, 1909) and William James to James Watson (James, 1911; Watson, 2007). Two very different classes of theories have been proposed to account for episodic recognition memory: *Dual Process theories*, which propose that recognition relies on two distinct memory processes, and *Single Process theories*, which assume recognition reflects the assessment of a single underlying memory strength signal.

Theories of Recognition

**Dual Process Models.** The distinction between *re-collection* and *familiarity* underlies several contemporary theories of human memory, e.g., (Atkinson & Juola, 1974; Jacoby & Dallas, 1981; Mandler, 1980; Yonelinas, 1994) and has played a critical role in characterizing memory impairments in amnesia, e.g., (Aggleton & Shaw, 1996; Huppert & Piercy, 1976; Norman & O'Reilly, 2003). Central to these theories is the claim that recognition memory judgments can be based on two distinct memory retrieval processes. The *familiarity* process is generally assumed to reflect the rapid assessment of global familiarity or memory strength of an item. The idea is that recently encountered items will seem more familiar than novel items, thus subjects can accept the more familiar items as having been studied. Familiarity is generally assumed to reflect a signal detection process as in Figure 1A such that familiarity strength is directly related to recognition confidence. Recognition memory judgments, however, are not limited to assessments of familiarity. If a subject can recollect some aspect of the study episode (e.g., where or when the event
occurred), this can also serve as a basis for recognition judgments. The recollection process is generally assumed to reflect a search of memory similar to that used in free recall whereby associative information about the study event is retrieved. As such, recollection is expected to support relatively high confidence recognition responses, as illustrated in Figure 1A. In addition, because recollection provides associative information about previous study events it is expected to be particularly useful in tests of source recognition in which subjects are required to retrieve where or when items were previously studied.

A number of recent dual process models have assumed that recollection depends critically on the hippocampus, which is responsible for binding the different aspects of a study event together, whereas familiarity relies on regions surrounding the hippocampus such as the perirhinal cortex which are assumed to be involved in the identification of individual items in the environment (Aggleton & Brown, 1999; Eichenbaum, 1994; Norman & O'Reilly, 2003). Thus, dual process models predict that recollection and familiarity should be functionally dissociable, and should exhibit distinct physiological correlates. In addition, patients with damage limited primarily to the hippocampus should exhibit deficits in recollection, but not familiarity, whereas patients with damage to the hippocampus and the adjacent MTL regions should exhibit deficits in recollection and familiarity.
Single Process Models. The leading alternative account to dual process models are single process theories, which assume that recognition relies on a single underlying memory strength signal, e.g., (W. Donaldson, 1996; Dunn, 2004). One example is the unequal variance signal detection model illustrated in Figure 1B. Although many different types of information could contribute to the memory signal, according to this model all recognition responses are based solely on the assessment of the overall memory strength signal. The old items are on average more familiar than new items, but they are also associated with greater variance than the new items (i.e., the old item distribution is wider than the new item distribution). According to these models, the strongest items are experienced as recollected, whereas weaker items are experienced as familiar. Thus, recollected and familiar items differ only in strength and thus they are not expected to be functionally or physiologically dissociable.

One single process account of the medial temporal lobes is the declarative memory model (Squire, 2004; Squire & Wixted, 2011; Squire, Wixted, & Clark, 2007), which assumes that the medial temporal lobes are critical for all forms of declarative/explicit memory including both recollection and familiarity, and that each subregion within the medial temporal lobes is equally important for both processes. Thus, according to this model recollection and familiarity should differ only in strength, and so their physiological correlates should be similar and differ only in magnitude. In addition, lesions to any medial temporal lobe region should produce deficits in both recollection and familiarity in a graded manner related to the size of the MTL lesion. Note that hybrid models which assume that recollection and familiarity are distinct processes that collapse into a single strength measure have been proposed, e.g., (Rotello, Macmillan, & Reeder, 2004). Although these models do
not make claims about the brain, because they maintain the distinction between recollection and familiarity, they could account for the same results as the dual process models.

**Data Review, Critical Debates, & Unresolved Issues**

**Cognitive & Behavioral Approaches**

Several different behavioral methods have been developed to measure recollection and familiarity, but a combination of source memory and ROC methods has proven particularly useful. One common method to assess recollection and familiarity is the “Remember/Know” (R/K) paradigm (Tulving, 1985), in which subjects indicate whether items are recognized on the basis that subjects either “Remember” contextual information about the study event, or they simply “Know” they have seen that item earlier. Although this method has proven useful in some contexts (Gardiner, Ramponi, & Richardson-Klavehn, 1998, 2002; Gardiner, Richardson-Klavehn, & Ramponi, 1998), in many cases results from this paradigm can be accounted for by both single and dual process models (Dunn, 2004; Rotello, et al., 2004; Wixted & Squire, 2004; Wixted & Stretch, 2004). Additionally, R/K procedures can be confusing for subjects to understand and use correctly, particularly amnesics (Baddeley, Vargha-Khadem, & Mishkin, 2001). A more objective way of assessing recollection is to use source recognition tasks that require subjects to indicate the study list in which the items were encoded. If subjects are able to determine when or where an item was studied it is assumed they recollected this information.

Identifying familiarity using a source memory test has been more difficult, but see (Jacoby, 1991), but one useful method has been based on ROC methods. That is, subjects
indicate their recognition confidence for each item in a recognition test, and performance on old items (i.e., the hit rate) is plotted against performance on new items (i.e., false alarm rate) as a function of response confidence. Fitting the behavioral ROC to a dual process model produces estimates of recollection and familiarity, and these estimates have been validated using a variety of other measurement methods, e.g., (Yonelinas, 2001a, 2001b). In physiological studies, familiarity correlates are identified as those that increase monotonically with confidence across intervals 1-4 (Curran, DeBuse, Woroch, & Hirshman, 2006; Woodruff, Hayama, & Rugg, 2006). In addition, high confidence responses can be used as a rough index of recollection, or to further constrain source memory measures. ROC methods have just been applied to neuroscientific studies to assess single and dual process models (Fortin, Wright, & Eichenbaum, 2004; Sauvage, Fortin, Owens, Yonelinas, & Eichenbaum, 2008; Squire, et al., 2007), although only rarely have they been combined with source memory tasks, but see (Ranganath et al., 2004).

Behavioral studies have shown that recollection and familiarity are functionally distinct. For example, response deadline studies have indicated that recognition judgments that can be based on assessments of stimulus familiarity (e.g., old/new discriminations) can be made more rapidly than those that require recollection of qualitative information about the study event such as recognition of modality information (Hintzman & Caulton, 1997), source information (M. K. Johnson, Kounios, & Reeder, 1994), or associative information (Gronlund & Ratcliff, 1989). In addition, relaxing response criterion is associated with a gradual increase in the proportion of items accepted on the basis of familiarity, but has virtually no effect on the proportion of recollected items (Yonelinas, 1994), showing that the two processes are differentially sensitive to shifts in response criterion.
The opposite dissociation is provided by studies examining the effects of list length; increasing the number of items that the subject is required to remember leads to a decrease in recollection, but leaves familiarity relatively unaffected (Yonelinas & Jacoby, 1994). Finally, dividing attention at the time of encoding (Kelley, Jacoby, & Hollingshead, 1989) or at the time of retrieval (Jacoby, 1991) selectively disrupts recollection. The behavioral dissociations between recollection and familiarity have been taken as evidence in favor of dual process models and against single process models that require post hoc modifications to account for these results, for review see (Diana, Reder, Arndt, & Park, 2006). In addition, the finding that encoding manipulations and test manipulations can dissociate recollection and familiarity suggests that both the encoding processes and retrieval processes supporting these types of recognition response are at least partially distinct.

Neuropsychological Patients

Some neuropsychological studies have suggested that recollection and familiarity are neurally dissociable, but none of these studies have provided direct physiological measures of these processes. Studies of classic amnesia have indicated that patients with extensive medial temporal lobe damage (i.e., lesions that include both the hippocampus and the surrounding parahippocampal gyrus) exhibit deficits in recollection and familiarity (for reviews see (Eichenbaum, Yonelinas, & Ranganath, 2007; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998). These results, however, are consistent with the predictions of both the single and dual process models discussed above. More informative have been studies of mild hypoxics, who are patients who have experienced brief oxygen deprivation (3-5 minutes, typically from cardiac arrest). Although severe hypoxia can lead to widespread
cortical damage, mild cases appear to lead to relatively selective hippocampal damage (Di Paola et al., 2008; Zola-Morgan, Squire, & Amaral, 1986).

Using a variety of memory tests including remember/know and ROC procedures Yonelinas et al., (2002) demonstrated that mild hypoxic patients showed deficits in recollection, but that familiarity was intact relative to controls (Yonelinas et al., 2002). In contrast, stroke patients and temporal lobectomy patients who had extensive MTL damage that included the hippocampus and the surrounding parahippocampal gyrus exhibited deficits in recollection and familiarity. These dissociations provide support for the dual process models which predict that recollection and familiarity can be neurologically dissociated. In addition, to the extent that the hypoxic patients had damage that was relatively selective to the hippocampus compared to the stroke and temporal lobectomy patients, the results are consistent with the models assuming that the hippocampus is critical for recollection whereas the surrounding cortex is critical for familiarity.

However, results from another laboratory examined hypoxic patients using a remember/know procedure and found evidence that these patients exhibited deficits in both recollection and familiarity (Manns, Hopkins, Reed, Kitchener, & Squire, 2003). Various differences in procedures complicate the comparison of these two studies, but most importantly, in both studies recollection and familiarity were assessed using only behavioral paradigms (i.e., other than the behavioral measures no physiological measures of recollection and familiarity were obtained), and the latter study used only the remember/know procedure, which is a subjective report procedure that may be poorly suited to amnesic patients (Baddeley, et al., 2001). Critical in assessing the memory deficits in these patients will be studies that use more
objective behavioral measures of recollection and familiarity, and studies that provide independent physiological measurements of recollection and familiarity.

**Electrophysiological Effects of Episodic Memory Processes**

Distinct ERP correlates of recollection and familiarity during retrieval have been identified in healthy subjects (Curran, 2000; Friedman, 2000; Friedman & Johnson, 2000; Leynes, Landau, Walker, & Addante, 2005; Rugg & Curran, 2007; Rugg, Mark, et al., 1998). ERP studies of healthy subjects have indicated that at time of retrieval, familiarity is associated with an enhanced positivity relative to new words spanning 400-600ms post stimulus onset, referred to as the FN400 (Figure 2). The N400 is very commonly elicited ERP component in receptive language paradigms, and related to semantic processing load (Curran, Tucker, Kutas, & Posner, 1993; Kutas & Federmeier, 2011; Kutas, Neville, & Holcomb, 1987), but this “semantic N400” is typically more posterior than the “familiarity N400”, which tends to be more anterior and distributed maximally at the mid frontal electrodes. As a distinct familiarity signature of memory, it is often referred to as the FN400 or mid-frontal old/new effect in order to distinguish from the classic “semantic N400” that is observed more posteriorly in language studies. In contrast, recollection has been linked with a separate Late Parietal Component (LPC) (Figure 2), which is a positive going waveform
that is typically greater for recollected items than for familiar old or new items. The LPC has an onset that emerges approximately 600ms post stimulus, lasting at least until 800ms, and has traditionally been maximal over left parietal sites (Curran, 2000; Curran, Tanaka, & Weiskopf, 2002; Rugg, Mark, et al., 1998; Wilding & Rugg, 1996).

In studies of memory retrieval, results from a wide variety of paradigms have linked the LPC and FN400 to recollection and familiarity, respectively. For example, the LPC and FN400 have been related to Remember and Know responses, respectively, e.g., (Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Rubin, Van Petten, Glisky, & Newberg, 1999; M. E Smith, 1993; Woodruff, et al., 2006). In addition, as illustrated in Figure 3, deeply encoded items and shallowly encoded items produce similar FN400s relative to new items, whereas deeply encoded items exhibit a larger LPC relative to both shallowly encoded and new items (Rugg, Mark, et al., 1998). Because recollection is expected to benefit preferentially from deep encoding the results suggest the LPC and FN400 are related to recollection and familiarity, respectively. Furthermore, the LPC is associated with recognition responses in which subjects accurately retrieve source information, whereas the FN400 has been related to recognition responses for which source memory fails (Curran, 2000; Curran, et al., 2006). Finally, the FN400 has been shown to vary monotonically with levels of confidence during recognition tests (Curran & Hancock, 2007; Woodruff, et al., 2006) and with the amount of information retrieved - even in the absence of conscious memory (Curran, et al., 2006; Duzel, et al., 1997) – thus offering an electrophysiological compliment to the behavioral data, which suggests that familiarity functions as a graded memory signal strength based on criterion setting.
The finding of spatially and temporally distinct ERP correlates of recollection and familiarity based responses provides strong evidence for the predictions of dual process models, and can only be accounted for by the single process models if they adopt additional post hoc assumptions (Diana, et al., 2006; Yonelinas & Parks, 2007). Although ERPs do not provide sufficient spatial resolution to determine which brain regions are responsible for generating those correlates, and it is unlikely that these scalp ERPs reflect direct medial temporal lobe activity, the spatially distinct patterns of activity demonstrate that the neural generators of these two processes must be at least partially distinct (Duzel, et al., 1997; Rugg & Curran, 2007; Rugg, Mark, et al., 1998).

**Electrophysiology of Neuropsychological Patients**

ERPs have been used to examine overall recognition in a variety of different patients, but they have not yet been used to examine recollection and familiarity in these neuropsychological amnesic patients. For example, Rugg et. al. (Di Paola, et al., 2008) examined recognition retrieval related ERPs in a group of temporal lobectomy patients and found that the old/new retrieval effects were significantly reduced in these patients (also see (M. E. Smith & Halgren, 1989). In addition, Olichney et al. (Olichney et al., 2000) examined memory related ERPs in a group of amnesic MTL patients and found evidence that an N400 ERP component was intact in amnesics whereas the LPC was significantly reduced. Although these studies were not designed to assess recollection and familiarity, the results are particularly interesting in suggesting the potential dissociation of memory ERPs in mild amnesia patients whom have shown behavioral dissociations of recollection and familiarity, albeit contentiously (Wixted & Squire, 2004; Yonelinas et al., 2004).
Another recent study examined ERPs in a single hypoxic patient during a continuous recognition task (Lehmann, Morand, James, & Schnider, 2007) and showed that the patient exhibited an attenuated old/new ERP effect. Finally, one other single patient study (Duzel, Vargha-Khadem, Heinze, & Mishkin, 2001) examined ERPs in a developmental hypoxic-amnesia patient with selective hippocampal pathology (Gadian et al., 2000; Vargha-Khadem et al., 1997), and showed a preserved FN400, followed by attenuated LPC (see similar results of Mecklinger et. al.(Mecklinger, von Cramon, & Matthes-von Cramon, 1998) for effects of more extensive hypoxia). However, none of these previous studies has directly assessed recollection and familiarity, so it is unclear how the ERPs observed in these patient studies are related to recollection and familiarity. Essential in understanding the effects of amnesia on recollection and familiarity will be patient studies that combine both ERP and behavioral measures of these memory processes.

As noted in (Addante, Watrous, Yonelinas, Ekstrom, & Ranganath, 2011; Rugg & Curran, 2007) , although it is unlikely that the ERP correlates of recollection and familiarity measured on the scalp reflect direct measures of MTL sub-regions because the hippocampus is neuroanatomically arranged as a closed electrical field and thus electrically neutral when recording outside of it, there is good reason to suspect that MTL regions do play a critical role in the modulating the brain networks that are involved in producing these ERPs. As early as 1986, Smith, Stapleton, and Halgren suggested that “MTL-N4” and MTL-P3” single unit potentials evoked in the MTL exhibited qualitatively distinct characteristics that similarly reflected those of scalp recorded potentials (Farovik, Dupont, Arce, & Eichenbaum, 2008). Heit, Smith, and Halgren showed with single unit recordings that MTL patients displayed attenuated old/new effects which were consistent with the timing of cortical old/new effects
during repetition (Heit, Smith, & Halgren, 1988), while Fernandez showed similar effects of encoding differences in the hippocampus and the rhinal cortex (Fernandez et al., 1999).

These single unit potentials recorded within the medial temporal lobe (Fernandez, et al., 1999; Heit, et al., 1988), are similar in time course to scalp recorded potentials (Rugg & Curran, 2007), and cortical ERPs (i.e.: P300) have been attributed to medial temporal lobe regions (Klimesch, Doppelmayr, Schwaiger, Winkler, & Gruber, 2000), likely due to cortico-hippocampal re-entrant loops, c.f. (Miller, 1991), [for similar empirically-grounded interpretations of effects see (Guderian & Duzel, 2005; Guderian, Schott, Richardson-Klavehn, & Duzel, 2009)].

Indeed, animal fiber-tracing studies (Saleem, Kondo, & Price, 2008; Suzuki & Amaral, 2004) have shown anatomical connections between medial frontal cortex and the entorhinal cortex (both thought critical for familiarity effects), while in humans hippocampal and parahippocampal functional connectivity with the lateral and medial parietal cortex (Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008; Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005) has been linked (each thought to serve recollective processing). Functional connectivity analysis and DTI have also revealed memory specific connectivity between the medial parietal cortex and the medial temporal lobe (Takahashi, Ohki, & Kim, 2008), and the connectivity networks of the PHc receiving ‘contextual’ information from polymodal parietal regions, and the perirhinal cortex receiving more unimodal projections of “what” feature-based processing(Fernandez & Tendolkar, 2006), are compelling as anatomical pathways for item (‘what’; familiarity) and source (‘context’; recollection) between the MTL and the cortex (Diana, Yonelinas, & Ranganath, 2007; Eichenbaum, et al., 2007) (Miller, 1991; Simons & Spiers, 2003).
The Effect of Pre-stimulus Activity & the Role of Theta Oscillations

Research on the neural basis of human memory has generally proceeded from the assumption that memory retrieval is driven by incoming stimuli that cue recovery of past experiences. However, recent research suggests that fluctuations in neural activity prior to stimulus presentation can also play a critical role in determining how a stimulus will be processed (Fox, Snyder, Vincent, & Raichle, 2007; Mazaheri, Nieuwenhuis, van Dijk, & Jensen, 2009; Raichle, 2009; van Dijk, Schoffelen, Oostenveld, & Jensen, 2008). For example, synchronous electrophysiological activity observed just prior to stimulus presentation has been found to modulate behavior on psychophysical, conditioning, motor, and attentional tasks (Linkenkaer-Hansen, Nikulin, Palva, Ilmoniemi, & Palva, 2004; Makeig et al., 2002; Mazaheri, et al., 2009; Seager, Johnson, Chabot, Asaka, & Berry, 2002; Wyart & Tallon-Baudry, 2009). It is unclear, however, whether other cognitive functions such as episodic memory retrieval are influenced by pre-stimulus neural activity.

Previous research has shown that cueing subjects to retrieve from memory leads to sustained changes in neural activity (Duzel et al., 1999; Duzel et al., 2001; Grady, McIntosh, Beig, & Craik, 2001; Herron & Wilding, 2004; Lepage, Ghaffar, Nyberg, & Tulving, 2000; Nyberg et al., 1995). These results indicate that brain networks are sensitive to the intention to retrieve from memory, but it is not known whether this neural activity has any impact on memory retrieval. Evidence from event-related potential (ERP) studies indicates that the intention to retrieve might not be related to successful memory retrieval (Herron & Wilding, 2004; Morcom & Rugg, 2002). However, an examination of oscillatory brain activity, rather than sustained activity may prove more useful in revealing such retrieval effects.
Computational models suggest an important role for theta oscillations (4-8hz) in memory functions (Lisman & Idiart, 1995), particularly in the rodent hippocampus (Buzsaki, 2002; Hasselmo, Bodelon, & Wyble, 2002; Hasselmo & Eichenbaum, 2005), a region which has been shown to also be particularly important for humans in source recognition (Eichenbaum, et al., 2007). In addition, results from studies using scalp and intracranial electroencephalography (EEG) suggest that cortical theta activity during stimulus presentation may be correlated with successful episodic memory (Klimesch, et al., 2000; Nyhus & Curran, 2010; Sederberg, Kahana, Howard, Donner, & Madsen, 2003), and that theta oscillations prior to initial stimulus presentation are associated with more effective encoding (Guderian, et al., 2009).

The Current Project:

These studies will examine recognition memory in healthy controls and amnesic patients. Experiment 1 aims to determine whether pre-stimulus EEG activity is predictive of subsequent recognition memory. In Experiment 2, the ERP correlates of recollection and familiarity in healthy young subjects are explored during retrieval to determine whether high and low confidence source recognition reflect recollection. Experiment 3 aims to determine how recollection and familiarity are influenced in amnesia. In the current experiments we will use a combined item & source method to provide behavioral measures of recollection and familiarity that overcomes limitations associated with prior subjective report procedures. The experiments will also allow us to directly address several critical gaps in the empirical literature, and will be essential in resolving several current theoretical debates about the nature of memory:
First, as discussed earlier, dual- and single-process theories make different predictions regarding whether recollection and familiarity will be related to similar or dissociable physiological signals. ERP measures provide an ideal physiological index of recollection and familiarity because of their high temporal resolution, and previous studies have suggested that they are useful in separating these processes during retrieval. Thus, the proposed ERP studies will prove useful in testing the conflicting predictions of single- and dual-process models.

Second, it is unknown whether differences in recollection and familiarity observed at time of retrieval might be related to differences in brain states that precede and possibly influence how the memory stimuli are remembered by the subject, and current models have focused primarily on elucidating the mechanisms operating at time of retrieval – not the role of on-going fluctuations of neural activity. ERP measures of recollection and familiarity will be obtained to determine whether differences during pre-stimulus and retrieval periods can be observed. These results will indicate the extent to which current models need to be modified to incorporate brain states at the time of retrieval which may influence memory success.

Third, it is currently debated whether – and how- recollection and familiarity are disrupted in amnesic patients, but no previous study has examined behavioral and physiological measures in the same patients. We will assess recollection and familiarity in these patients using novel item & source behavioral methods, as well as measuring the ERP correlates of these processes in amnesic patients. These results will be useful in testing the conflicting predictions of dual process and single process
theories, and will be essential in characterizing the memory impairments of these different patient groups.

This experimental approach addresses several theoretically important questions about the processes underlying episodic recognition memory (e.g., Are there one or two processes underlying recognition memory? How are these processes impaired in amnesia? Are these impairments related to retrieval problems or fundamental differences in existing brain states?).

ERPs of recognition processes in amnesia can critically, albeit indirectly, inform a debate about which memory processes are supported by the hippocampus, and which are not dependent upon the hippocampus (to that extent that mild hypoxia results in a damage restricted to the hippocampus (Di Paola, et al., 2008), and that the LPC and FN400 correlated with recollection and familiarity-based processing, respectively, i.e.: (Rugg & Curran, 2007).

These series of experiments utilize powerful new behavioral methods which combine item and source memory tasks that overcome limitations of previous methods. They also represent the first time that scientists have investigated the role of pre-stimulus oscillations during memory retrieval tests. In addition, it applies these methods for the first time in ERP studies of patients with MTL damage, towards characterizing the neural organization of memory.
Research Design: General Questions, Specific Aims, & Overall Design

At a broad level, the ensuing three chapters will address three general questions about the fundamental nature of human memory:

1. How does it work? – What conditions are needed for engaging memory networks?
2. What is it made of? – What processes enable us to experience “Mental Time Travel”?
3. How is it organized in the brain - What goes wrong in certain types of amnesia?

These general questions will be returned to in the concluding remarks, informed by the results of what was observed in the following series of experiments.

We addressed the general questions above by focusing on the following two specific aims:

Aim 1- In healthy young subjects:

   a) Identify the EEG correlates of recollection and familiarity during retrieval using combined item and source memory methods.

   b) Explore the contribution that pre-stimulus neural activity plays in interacting with stimulus-driven brain activity in supporting accurate source memories.

Experiments 1 & 2 will examine the ERP correlates of recollection and familiarity during a memory test. Healthy young subjects will first study words from two encoding sources, and then be tested on their item recognition and source memory using 5-point confidence scales. A critical debate in the memory literature revolves around the adequacy of single and dual process models of recognition. The later models predict that during retrieval, familiarity should be related to an ERP memory signal which both occurs earlier and exhibits distinct scalp topography than that of recollection, thus offering neurophysiological assays of cognition to address which cognitive process may support certain memory conditions.
ERP methodology is ideally suited for examining this issue because it provides both a direct physiological measure of the complex neural processes involved in recognition retrieval, as well as providing information with very high temporal resolution – a characteristic that is particularly important in separating cognitive processes expected to exhibit rapid temporal dynamics - which is difficult for other techniques, such as fMRI to capture. Another particular strength of ERPs is that they facilitate the concurrent use of precise behavioral paradigms, such as confidence responding and source recognition we will utilize, in order to objectively quantify the specific contributions of recollection and familiarity during memory processing. During retrieval we expect to find recollection and familiarity responses to be related to distinct ERP components (i.e., the LPC and FN400, respectively) which would provide support for the dual process models of recognition.

In addition, we will also explore the EEG data for differences in brain activity that is occurring before the retrieval cue is presented to the subject during the memory test, in order to assess if differences in states of brain activity prior to a cognitive task are influential in the success of the ensuing memory probe. Time-frequency decomposition will be used for this, in order to explore the power spectrum of different frequency bands, with an apriori focus on theta (4-8Hz) band activity as playing a fundamental role in memory processing (Guderian, et al., 2009; Hasselmo, Bodelon, et al., 2002; Nyhus & Curran, 2010).

**Aim 2- Identify the ERP correlates of memory processes in hypoxic amnesia patients to determine which episodic memory processes are impaired and intact.**

Experiment 2 will use the same methods as Experiment 1, but will examine recognition memory in three amnestic patients (H) and six healthy control subjects (C). This
is the maximum number of chronic amnesia patients available who meet our inclusion criteria (for review, see (Di Paola, et al., 2008), p.719). The general aim is to test the prediction that the mild hypoxic amnesia patients exhibit a selective deficit in recollection. These predictions will be assessed by a) examining the behavioral measures of recollection and familiarity derived from the source and item memory responses, and b) examining the ERP correlates of recollection and familiarity. Since the validity of behavioral and hemodynamic measures of recollection and familiarity forms of memory have both been questioned (Mickes, Wixted, & Wais, 2007; Song, Wixted, Smith, & Squire, 2011; Wixted & Squire, 2004; Yonelinas, et al., 2004), we will make use of ERP recordings of the direct neural activity for the memory processes serving recognition memory.
Chapter 2: Pre-stimulus Theta Activity Predicts Source Memory Retrieval

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Abstract

Recent evidence indicates that the processing of a stimulus can be influenced by preceding patterns of brain activity. Here, we examined whether pre-stimulus oscillatory brain activity can influence the ability to retrieve episodic memories. Neural activity in the theta frequency band (4-8 Hz) was enhanced prior to presentation of test items which elicited accurate recollection of contextual details of the prior study episode (‘source retrieval’), relative to trials for which item recognition was successful but source retrieval failed. Post-stimulus theta activity was also related to source retrieval, and the magnitude of post-stimulus theta was predicted by the magnitude of the pre-stimulus theta effects. The results suggest that on-going neural processes occurring prior to stimulus onset might play a critical role in readying the brain for successful memory retrieval.
Introduction

Research on the neural basis of human memory has generally proceeded from the assumption that memory retrieval is driven by incoming stimuli that cue recovery of past experiences. However, recent research suggests that fluctuations in neural activity prior to stimulus presentation can also play a critical role in determining how a stimulus will be processed (Fox, et al., 2007; Mazaheri, et al., 2009; Raichle, 2009; van Dijk, et al., 2008). For example, synchronous electrophysiological activity observed just prior to stimulus presentation has been found to modulate behavior on psychophysical, conditioning, motor, and attentional tasks (Linkenkaer-Hansen, et al., 2004; Makeig, et al., 2002; Mazaheri, et al., 2009; Seager, et al., 2002; Wyart & Tallon-Baudry, 2009). It is unclear, however, whether other cognitive functions such as episodic memory retrieval are influenced by pre-stimulus neural activity.

Previous research has shown that cueing subjects to retrieve from memory leads to sustained changes in neural activity (Duzel, et al., 1999; Duzel, Picton, et al., 2001; Grady, et al., 2001; Herron & Wilding, 2004; Lepage, et al., 2000; Nyberg, et al., 1995). These results indicate that brain networks are sensitive to the intention to retrieve from memory, but it is not known whether this neural activity has any impact on memory retrieval. Evidence from event-related potential (ERP) studies indicates that the intention to retrieve might not be related to successful memory retrieval (Herron & Wilding, 2004; Morcom & Rugg, 2002). However, an examination of oscillatory brain activity, rather than sustained activity may prove more useful in revealing such retrieval effects. Computational models suggest an important role for theta oscillations (4-8hz) in memory functions (Lisman & Idiart, 1995), particularly in the rodent hippocampus (Buzsaki, 2002; Hasselmo, Bodelon, et al., 2002;
Hasselmo & Eichenbaum, 2005), a region which has been shown to also be particularly important for humans in source recognition (Eichenbaum, et al., 2007). In addition, results from studies using scalp and intracranial electroencephalography (EEG) suggest that cortical theta activity during stimulus presentation may be correlated with successful episodic memory (Klimesch, et al., 2000; Nyhus & Curran, 2010; Sederberg, et al., 2003), and that theta oscillations prior to initial stimulus presentation are associated with more effective encoding (Gudarian, et al., 2009).

Here, we examined whether neural activity that occurs prior to the presentation of a retrieval cue would predict whether the item would elicit successful episodic retrieval (Figure 1). Seventeen healthy college-aged subjects encoded a series of words by making pleasantness or animacy judgments. After a short delay they were presented with a mixture of studied and novel words and indicated whether the item was old or new (“item memory”) as well as the context in which the item had been encountered (“source memory”). Prior work has indicated that item and source recognition discriminations recruit distinct brain regions (Ranganath, Heller, & Wilding, 2007; Weis et al., 2004) and may be supported by different cognitive processes (Yonelinas, 2001a), but it is not known whether ongoing oscillatory activity before the onset of a retrieval cue can influence the likelihood of successful item or source retrieval. To address this issue, we recorded scalp EEG during a test of item and source memory, and analyzed pre-stimulus activity as a function of whether the test item elicited successful recollection responses.

**Methods**

**Subjects, Stimuli, and Procedure:** Seventeen right-handed undergraduate students (9 males) were recruited from the University of California–Davis Psychology Department
subject pool, and received credit for participation. Subjects were free from neurological, visual, motor, or other medical disorders, and the experiment was conducted as approved by the University of California – Davis IRB protocol for research on human subjects. Word stimuli were presented in uppercase letters in a white font (size 36), centered on a black background screen (Figure 1). Each stimulus was only presented once during both study and test. Subjects were seated 44 inches away from the screen.

During study, subjects encoded 200 words (presented in 4 lists of 50 words each) during an incidental encoding task. Two separate encoding tasks (i.e., Pleasantness and Animacy judgments), were used, which served as the basis for source memory decisions during retrieval (i.e., indicate if each item is pleasant or not, ‘yes’ or ‘no’; is this item “Alive” in real life, ‘yes’ or ‘no’). These encoding tasks were selected to lead to roughly comparable levels of memory. The two encoding tasks were presented in a blocked ABBA design, counterbalanced between subjects for the order of the two tasks. Prior to each study block, the instructions for next task was read to the subject, and there was a practice session of 10 stimuli that the experimenter and subject performed together in order to be sure that the subject completely understood the task and was performing it correctly. None of the practice stimuli appeared in the test phase. There was a fifteen-minute filler task before the retrieval phase of the experiment commenced.

During retrieval, the 200 stimuli presented during the encoding phase were randomly intermixed with 100 new words (lures), for a total of 300 test stimuli (Figure 1). The test stimuli were presented in 6 test sessions of 50 stimuli each. Prior to each stimulus presentation, a fixation cross appeared in the middle of the screen for 1000ms, during which subjects were instructed not to blink, so as to minimize ocular artifacts in the EEG. The
retrieval probe then appeared on the screen for 1500ms, during which time the subject viewed the stimuli, but were not yet cued to respond (Figure 1). Subjects were also instructed not to blink while each stimulus was on the screen. After the 1500ms probe, subjects were asked first to make an item recognition judgment followed by a source recognition judgment; each of these responses was subject paced and therefore provided a variable temporal jittering of each subsequent stimuli’s presentation.

For item recognition judgments, subjects responded on a 5-point confidence scale, with 5 indicating that they were sure it was old, 4 that it was probably old, 3 that they were guessing, 2 that it was probably new, and 1 that they were sure it was new. Studied items that received a 5 or 4 response were treated as ‘correct item’ recognition trials. For source recognition judgments, subjects also responded on a 5-point scale with 5 indicating that they were sure it was from the animacy encoding task, 4 that it was probably from the animacy task, 3 that they were guessing, 2 that it was probably from the pleasantness task, and 1 indicating they were sure it was from the pleasantness task. ‘Correct source’ memory trials included the items studied under the animacy encoding conditions that received 5 or 4 responses and the items studied under the pleasantness encoding conditions that received 1 or 2 responses. Guess responses weren’t included in EEG analysis.

**EEG Acquisition and Analysis:** EEG was recorded using a BioSemi ActiveTwo Recording System with a 32 channel electrode cap conforming to the standard International 10-20 System of electrode locations, sampled at a rate of 1024hz. Subjects were instructed to minimize jaw and muscle tension, eye movements, and blinking. EOG was monitored in the horizontal direction and vertical direction, and this data was used to eliminate trials contaminated by blink, eye-movement, or other artifacts.
All EEG analyses were performed using custom Matlab code and functions from the EEGLab Toolbox for Matlab (Delorme & Makeig, 2004). Raw EEG data was re-referenced to average mastoids, downsampled to 512 Hz, and high-pass filtered at .5 Hz in order to optimize independent component analysis (ICA) decomposition. These data were epoched from 1.25 seconds before the onset of the retrieval item to 2.4 seconds following the retrieval item, and was baseline subtracted from -200 to 0 ms. This step was necessary for artifact rejection and correction, because trial-to-trial variability in DC offsets can make it difficult to detect artifacts. Baseline correction in the time domain effectively amounts to subtracting a scalar and therefore should have no impact on frequency components. Epochs containing single channel data exceeding 3 standard deviations of the channel’s mean across epochs were removed to optimize ICA decomposition, as were epochs containing data 5 standard deviations from the pooled channel mean. This procedure was designed to remove primarily non-biological noise, while allowing “common” artifacts (such as eye-blinks) to remain. Data were then decomposed into temporally independent components using Infomax ICA (Bell & Sejnowski, 1995). Artifactual components (eye-blinks, muscle tension, etc) were removed by hand, as were any remaining noisy epochs.

Single subject pre-processed EEG data was next subject to spectral decomposition using wavelets. Wavelet analysis provides an estimate of the power of a signal with good spectral and temporal resolution (van Vugt, Sederberg, & Kahana, 2007). Spectral power was computed from 4-50 Hz by convolving a Morlet wavelet (cycles = 5.7) with the observed signal at each electrode site. After accounting for edge artifacts associated with time-frequency analysis, we obtained power values from -450 to 900ms for each stimulus. Spectral domain baseline subtraction was not performed because the pre-stimulus window,
used most commonly for this procedure, is the time of interest in this study. In order to reduce the number of statistical comparisons, we averaged the resulting spectrograms across time (150 ms time bins) and frequency band (theta: 4-8 Hz, alpha: 9-12 Hz, beta: 13-30 Hz; gamma: 31-50 Hz) prior to pooling the data across subjects. Further details of the statistical analysis and control analysis performed are available in the Supplemental Materials.

Results

Item recognition accuracy was high (i.e. the average hit rate (.80) was significantly greater than the false alarm rate (.18), p < .00001), and source memory accuracy for the items that were correctly recognized was above chance (i.e., the average proportion of correct source judgments for recognized items was .73, p<.0000001; see Figure S1 for response distributions). We were interested in whether theta activity prior to the onset of a retrieval cue was related to subject’s ability to recollect source details learned during the encoding session, and so as in previous ERP and functional imaging studies (Davachi, Mitchell, & Wagner, 2003; Guo, Duan, Li, & Paller, 2006; Ranganath et al., 2003; Wilding, Doyle, & Rugg, 1995; Wilding & Rugg, 1996), we compared trials with both an accurate item and source response (i.e. item correct and source correct, “Item+Source”) to trials receiving only an accurate item judgment (i.e. item correct and source incorrect, “Item-only”). Spectral power was estimated every 10ms from -450ms to 900ms (1350ms total), and the total epoch was then divided into nine 150ms bins. The pre-stimulus effects are first described, followed by post stimulus effects.

Memory differences in theta power were apparent prior to stimulus onset first at left temporal, and then across frontal and left lateralized regions of the scalp. Analyses of the difference between Item+Source and Item-only trials for the -300ms to -150ms time window
(see Fig. 2a) revealed significant differences at left temporal (T7) and left parietal (Cp5) sites (bootstrap-corrected p<.05 for both sites, procedure detailed in Supplemental Materials). During the -150 to 0 ms time window this effect became progressively more widespread (Fig. 2d), as theta power at left temporal, left parietal, and mid-frontal electrode sites was significantly higher for Item+Source than for Item-only trials (Figure 2d). Figures 2b and 2e show the time course of theta activity in each condition at representative left temporal (T7) and frontal electrodes (electrode Fz), respectively, along with the time-frequency spectrograms for the difference in oscillatory power between Item+Source and Item-only trials at these sites. Further analyses were conducted to determine whether theta phase alignment across trials differed between Item+Source and Item-only, but no significant effects were observed.

To determine whether the pre-stimulus theta modulation reflected a more generalized item recognition memory effect, we contrasted item hits against trials in which a studied item was incorrectly judged to be new (‘Item-incorrect’). This contrast did not reveal significant differences at any electrode site prior to stimulus onset (-150 to 0ms, all t-values <1.5, all p>.15). Thus, pre-stimulus theta appears to be predictive of accurate retrieval of study details rather than old/new recognition discriminations.

Could the pre-stimulus theta effects have been driven solely by post-stimulus theta activity, due to temporal imprecision of the wavelet analysis method? Several factors weigh against this possibility. First, there were no significant memory effects observed between 0 and 300ms post-stimulus, so it is unlikely that a pre-stimulus effect (-300 to 0ms prior to stimulus onset) could be produced by a temporal blurring of a later post-stimulus effect. Second, we varied the filter parameters of the wavelet analysis to increase temporal
resolution (by decreasing the wavelet cycles from 5.7 to 3 or 1 wavelet cycles, see Supplemental Materials for details), and the pattern of pre-stimulus memory effects was unchanged (significant at bootstrap-corrected levels of p<.05) (Figure S2). Third, in addition to the wavelet analyses, we conducted an analysis using a Fourier transform on the window from -450 to 0ms. This analysis, which specifically assessed activity restricted to the pre-stimulus period, also revealed a significant pre-stimulus memory effect (t(16)=1.92, one tailed p = .036). Finally, we conducted a series of simulations to quantify the extent of filter smearing produced by the wavelet analysis (Figure S3, see Supplemental Materials for details). These simulations revealed that a post-stimulus theta oscillation would result in a large post-stimulus difference and a relatively small pre-stimulus difference using the same 5.7 wavelet cycle analysis applied to the real data (Figure S3b, S3c), and that this would be eliminated in using a 1-cycle wavelet analysis (i.e.: Figure S2). In contrast, the source memory effect that we observed was large during the pre-stimulus period and diminished during the post-stimulus period (Figure 2d, 2e), which is consistent with our simulation of what would be expected if the effect was driven solely by pre-stimulus activity (Figure S3a, S3c).

Because correct source decisions are typically associated with confident item recognition judgments (Yonelinas, 2001a), it is possible that the pre-stimulus theta increases described above influenced the likelihood of making a confident response, rather than being specifically related to accurate source memory retrieval. To assess this possibility, we examined pre-stimulus theta activity preceding correct rejections as a function of response confidence using the same wavelet analysis procedure that was used in the source memory analysis described earlier. We did not find any significant pre-stimulus theta differences
between high- and low-confidence correct rejections, which suggests that pre-stimulus theta activity was related to memory retrieval, rather than confidence per se.

We next examined whether individual differences in source memory accuracy were correlated with the magnitude of the pre-stimulus theta source memory effects we observed from -300 to -150 ms (Fig. 2a) and -150 to 0 ms (Fig. 2d) (details in Supplemental Materials). As shown in Figure 2c, the initial pre-stimulus theta differences between conditions at left temporal sites (-300 to -150 ms, i.e.: Fig. 2a) were not significantly correlated with behavioral measures of source memory accuracy ($r^2 = .13; p = .62$). However, during the next pre-stimulus period of -150 to 0 ms (i.e. Figs. 2d & 2e) theta power differences between source memory conditions at frontal electrode Fz were positively correlated with individual differences in source memory accuracy ($r^2 = .36; p < .01$; similar effects were observed at other frontal electrodes, though not for left parietal or temporal electrodes during the pre-stimulus periods). The results suggest that, across subjects, pre-stimulus frontal theta activity directly relates to a subject’s ability to remember episodic details in response to a retrieval cue. To determine whether these differences might also be observed within subjects, we sorted all old trials (regardless of memory performance) for each subject into 5 equally sized bins based on the magnitude of theta. We found that, for the highest rank theta bin, there was a larger proportion of trials were item+source compared to item-only trials (i.e., $M=.19$ vs .15, respectively, ($t(32)=2.11$, $p<.05$), whereas for the lower ranking theta bins, there was no significant difference in the proportions of item+source and item-only trials (all $t(32)<1.02$, all $p>.31$). The latter results suggest that, even within subjects, higher pre-stimulus theta is predictive of accurate source memory.
Our next analyses focused on activity that occurred after the retrieval cue was presented. Consistent with previous studies that reported increases in theta power during successful episodic retrieval (Burgess & Gruzelier, 1997; T. Gruber, Tsivilis, Giabbiconi, & Muller, 2008; Guderian & Duzel, 2005; Osipova et al., 2006), we also found that post-stimulus theta activity was related to successful retrieval. As shown in Figure 3a, theta power at left parietal electrode locations between 450-600ms post-stimulus was significantly higher on Item+Source trials than on Item-only trials. Theta power time courses for Item+Source, Item-only, and Item-incorrect trials for a left parietal electrode (electrode P7), along with the time frequency spectrogram for the power difference between Item+Source and Item-only trials are presented in Figure 3b. Notably, this site showed both significant pre- and post-stimulus activity related to retrieval of source information. Correlational analyses revealed that participants who showed larger post-stimulus (300-450ms) theta effects at left parietal sites also showed higher source accuracy (Figure 3c; \( r^2 = .58, \ p = .014 \)).

One account of the preceding results is that theta activity prior to stimulus onset is related to a preparatory process that facilitates or enables the retrieval of episodic details when a retrieval cue is eventually presented. If so, then we might expect there to be a relationship between pre- and post- stimulus theta effects. To test this prediction, we measured the correlation between pre-stimulus theta effects (i.e., theta power difference between item+source and item-only trials during the pre-stimulus period of -300 to 0ms) at each electrode and post-stimulus theta effects at each electrode during 3 successive post-stimulus epochs (0 to 300ms, 300-600ms, and 600-900ms), while correcting for multiple comparisons (see Supplemental Methods for details). We found that the pre-stimulus theta
differences related to source retrieval at frontal sites predicted post-stimulus theta differences during the 300-600 ms time window (Figure 4b) at the left parietal site where we observed significant post-stimulus related memory related theta increases (see Figure 3a). These correlations were not significant in earlier (Figure 4a) or later (Figure 4c) time windows. This pattern of findings cannot be accounted for by volume conduction or temporal autocorrelation, because we did not observe frontal-left parietal theta difference correlations during the 0-300 ms time window (Figure 4a). Instead, these results suggest that frontal theta activity may influence post-stimulus theta activity at left parietal and temporal regions that is related to the recollection of episodic details.

**Discussion**

The present results demonstrate that oscillatory activity in the theta band prior to the onset of a retrieval cue was correlated with successful episodic retrieval. Specifically, pre-stimulus theta power was enhanced for items that were recognized and associated with correct source memory judgments, and larger pre-stimulus theta effects were also related to better source memory accuracy, both across subjects and across trials within a subject. This effect could not be attributed to a propensity to make more confident judgments, nor was it a generalized correlate of item recognition, because theta activity was specifically related to successful source retrieval. In addition, we found that post-stimulus increases in theta were related to source recollection, consistent with prior studies (Burgess & Gruzelier, 1997; T. Gruber, et al., 2008; Guderian & Duzel, 2005; Osipova, et al., 2006). Our study extends these findings to show that frontal pre-stimulus theta effects were significantly correlated with the left parietal post-stimulus effects, suggesting that preparatory processes may directly impact the later retrieval processes. These findings provide novel neural evidence for the idea
that episodic retrieval is not solely driven by retrieval cues, but rather that it reflects an interaction between cues and one’s preceding neurocognitive state.

These findings add to accumulating evidence indicating that pre-stimulus neural activity can influence performance on a number of different cognitive tasks (Linkenkaer-Hansen, et al., 2004; Makeig, et al., 2002; Mazaheri, et al., 2009; Seager, et al., 2002; Wyart & Tallon-Baudry, 2009). For example, several recent studies have shown that pre-stimulus neural activity is related to successful memory encoding (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; M. J. Gruber & Otten, 2010; Guderian, et al., 2009; Otten, Quayle, Akram, Ditewig, & Rugg, 2006; Otten, Quayle, & Puvaneswaran, 2010). Furthermore, conditioning rabbits during peaks of high theta activity leads to almost twice the levels of learning than during low theta periods (Berry & Thompson, 1978; Seager, et al., 2002). To our knowledge, however, no studies have investigated whether pre-stimulus oscillatory activity can influence successful episodic retrieval. We believe this may be because pre-stimulus activity is traditionally treated as noise in studies of episodic retrieval. For instance, in event-related potential (ERP) studies, the pre-stimulus baseline is usually subtracted out when averaging post-stimulus ERPs.

The precise functional relationship between pre-stimulus theta and memory retrieval is not yet clear, but our results suggest several possibilities that can be tested in future studies. One possibility is that pre-stimulus theta is related to fluctuations in attention or arousal that may benefit subsequent cue processing. Indeed, subjects were cued prior to presentation of each test item, and this could have led to an intentional increase in anticipatory attention. There are aspects of the data, however, that seem problematic for this account. For example, theta enhancements were not present for item-only trials or for
confident correct rejections. It is not clear why item recognition or the ability to reject unstudied items would not also benefit from enhanced attention. Other evidence against an attention account comes from studies reporting that theta suppression increased monitoring efficiency, whereas increases in theta resulted in poorer performance on attention tasks (Beatty, 1974). Furthermore, when pre-stimulus effects have been found for attention, they have been related to decreases in occipital alpha (Mazaheri, et al., 2009; O’Connel, 2009), rather than in increases in theta power, as observed here. We did not observe significant pre-stimulus differences in alpha power (8-12 Hz), nor was it correlated with behavioral measures of memory in ways that theta results were.

A second possibility is that pre-stimulus theta reflects a neurocognitive state that facilitates the processing of retrieval cues in a manner that can influence recollection (Rugg & Wilding, 2000b). For instance, fronto-parietal theta activity may have reflected the adoption of a “retrieval orientation”, which is a state that specifies the kind of information that is sought after when evaluating a retrieval cue (Rugg & Wilding, 2000b) (Herron & Wilding, 2004). This idea is broadly consistent with functional magnetic resonance imaging (fMRI) results reported by Quamme et al. (2010) indicating that activity in several brain regions may reflect whether participants are oriented to use recollection or familiarity as the basis for a memory decision. A related possibility is that pre-stimulus theta effects reflected the maintenance of an “episodic retrieval mode” (Lepage, et al., 2000). This might be conceived as a preparatory process by which the brain regions that are involved in episodic retrieval (e.g., frontal and parietal cortex; see (Buckner & Wheeler, 2001) are activated in anticipation of a retrieval cue. This proposal is consistent with the fact that theta was observed over left parietal sites both prior to stimulus onset as well as after stimulus onset,
and that the two effects were tightly coupled with source memory accuracy. If the retrieval mode account is correct, then theta power for correctly rejected new items should be intermediate between that seen for the item+source and the item-only trials. This is because correct rejections could occur on trials when the episodic retrieval mode is more engaged (i.e., high theta trials) and on trials when the retrieval mode is less engaged (i.e., low theta trials). In fact, a post hoc analysis indicated that, at both the frontal and left parietal sites, this was the pattern of results we observed.

A third possibility is that pre-stimulus theta reflects the re-instantiation of a contextual state that is similar to the contextual state at study (Polyn, Norman, & Kahana, 2009). Re-instantiation of contextual details such as spatial location (S. M. Smith, 1979), emotional state (Bower, 1981), or even state of intoxication (Goodwin, Powell, Bremer, Hoine, & Stern, 1969) can facilitate recall of items that were experienced in that context. Furthermore, the reinstatement of physical context cues has been shown to increase recollection-based recognition more so than familiarity-based item (Gruppuso, Lindsay, & Masson, 2007), which parallels the current finding that pre-stimulus theta was specifically enhanced for Item+Source trials, and not for Item-only trials.

In addition to characterizing the functional significance of the pre-stimulus theta effects observed here, it will be important to identify the brain regions that contributed to these effects. Our results are broadly consistent with computational models suggesting an important role for hippocampal theta oscillations (4-8hz) in memory functions (Buzsaki, 2002; Hasselmo, Bodelon, et al., 2002; Hasselmo & Eichenbaum, 2005) and more generally with findings suggesting that the hippocampus is critical for source recollection (Eichenbaum, et al., 2007). However, these models emphasize the importance of theta phase
for memory encoding and retrieval, and we did not observe significant changes in pre-stimulus theta phase alignment as a function of successful memory retrieval. In general, the role of the hippocampus in the generation of scalp-recorded theta remains to be characterized. It is unlikely that the effects that we observed at the scalp directly reflected volume conducted hippocampal field potentials, due to its neuroanatomical arrangement as a closed electrical field. Nonetheless, it is possible that the theta effects at left superior temporal sites 300ms prior to stimulus onset reflected cortico-hippocampal interactions (Benchenane, 2010; Fell & Axmacher, 2011; Jutras & Buffalo, 2010) that set the stage for memory retrieval. For instance, one possibility is that effective episodic retrieval is facilitated by pre-stimulus interactions between the hippocampus and left temporal cortex (-300 to -150ms), followed by left temporal, parietal, and frontal cortex. This pattern of pre-stimulus activity, in turn, may lead to enhanced post-stimulus theta synchronization between the hippocampus and left parietal and/or temporal cortex. Further work using invasive intracranial recordings, as well as experiments assessing the effects of hippocampal damage on patterns of scalp EEG, will be needed to assess this possibility.

Conclusions:

There are many factors that influence whether episodic memory retrieval will succeed or fail, including the way information was encoded, and the kinds of cues available during retrieval (Tulving & Thomson, 1973). The present results suggest that, in addition to such factors, fluctuations in brain activity prior to a retrieval cue might also influence how a cue will be processed. The results are consistent with the idea that theta oscillations play an important role in the dynamics of memory retrieval (Hasselmo, Hay, Ilyn, & Gorchetchnikov, 2002) and also open up new questions about the role of state-related
variables in memory (Rugg & Wilding, 2000b). Furthermore, it is conceivable that one might be able to increase the likelihood of episodic retrieval by inducing frontal theta oscillations prior to retrieval or by presenting retrieval cues during or immediately after periods of theta synchronization.
Tables & Figures

Figure 1. Schematic depiction of the memory retrieval paradigm.
Figure 2: Pre-stimulus theta is enhanced prior to successful episodic retrieval. (a) Bootstrap-corrected topographic significance map of pre-stimulus theta-band activity differences between Item Correct with Source Correct (“Item+Source”) and Item Correct with Source Incorrect (“Item-only”) items during the -300 to -150 ms time window. (Upper b) Average theta power time course for Item+Source, Item-only, and Item-incorrect trials for at the left posterior temporal electrode site T7. (Lower b) Item+Source vs Item-only difference spectrogram at electrode T7. (c) Relationship between theta differences at T7 during the pre-stimulus window (-300 to -150 ms window) and source memory accuracy. (d) Topographic significance map of pre-stimulus theta-band activity differences between Item+Source and Item-only trials during the -150 to -0 ms time window. (Upper e) Average theta power time course for Item+Source, Item-only, and Item-Incorrect trials for at the midfrontal electrode site Fz (labeled on 2a). (Lower e) Item+Source vs Item-only difference spectrogram at electrode Fz. (f) Relationship between theta differences at electrode Fz during the pre-stimulus window (-300 to -150 ms window) and source memory accuracy. Participants who showed larger pre-stimulus theta differences between Item+Source and Item-only trials at site Fz also showed higher source memory accuracy.
Figure 3: Post-stimulus parietal theta is enhanced during successful episodic retrieval. (a) Bootstrap-corrected topographic significance map of theta-band activity differences between Item+Source and Item-only trials during the post-stimulus (450 to 600 ms) time window. (Upper b) Average theta power time course for Item+Source, Item-only, and Item-incorrect trials for left parietal electrode P7. (Lower b) Item+Source vs Item-only difference spectrogram at electrode P7. (c) Relationship between theta differences at electrode P7 during the post-stimulus window (300 to 450 ms window) and source memory performance. Participants with larger post-stimulus theta differences between Item+Source and Item-only trials also showed higher source memory accuracy.
**Figure 4. Frontal pre-stimulus theta effects are correlated with parietal post-stimulus theta effects.** Topographic plot of correlations between pre-stimulus theta effects (-300 to 0 ms) and post-stimulus theta differences between electrodes during different post-stimulus time windows: 0-300ms (4a), 300-600ms (4b), and 600-900ms (4c). Significant correlations between electrodes at each latency are bootstrap-corrected for multiple comparisons (detailed in Methods). Arrows indicate a significant correlation, and direction of the arrow goes from pre-to-post stimulus correlation: arrow beginning indicates the pre-stimulus electrode; arrow end (i.e. arrowhead) indicates the post-stimulus electrode. The color scale indicates the magnitude of the Pearson’s correlation coefficient. Note the increased correlation (4B) between frontal pre-stimulus theta differences and left parietal post-stimulus theta differences during 300-600ms post-stimulus (compare to lower portion of Figure 3b).
**Supplementary Information**

**Statistical Analyses:** Power in each time-frequency bin at each electrode site was statistically compared between conditions using a bootstrapping procedure. Individual subject power values from 2 conditions were pooled across subjects and randomly assigned to one of two pseudo-conditions, which were compared with a paired-samples t-test. This procedure was repeated 5000 times creating a pseudo-t distribution. Selecting the t-value in the 2.5th and 97.5th percentile of the pseudo-t distribution provided a lower and upper critical t-value, respectively. Selection of a two-tailed bootstrap alpha level of 5% produces a type-I error rate of 1.6 electrodes out of 32 electrodes in any time-frequency window. Electrodes with an observed t-value greater than the upper critical-t value (or smaller than the lower critical t-value) in a given time-frequency window were deemed significant.

To assess relationships between theta activity and behavior, we correlated a behavioral measure of source memory accuracy (defined as the proportion of source correct trials minus the proportion of source incorrect trials) with theta activity difference scores. Relationships between pre-stimulus and post-stimulus theta differences were assessed using a bootstrapping procedure. Pairwise correlations (i.e. observed r-values) were calculated between pre-stimulus theta differences and post-stimulus differences at each combination of electrodes. To test spatial (i.e. frontal vs parietal) and temporal directionality (i.e. pre-stim vs post-stim), difference scores at each pair of electrodes were randomized into two pseudo-groups, and a pseudo correlation coefficient (i.e. pseudo r-value) was estimated. This process was repeated 1000 times at each pair of electrodes. All pseudo r-values were pooled and the pseudo r-value in the 95th percentile of the sorted distribution was taken as the critical r-value. All observed r-values greater than the critical r-value were deemed significant.
Control Analyses

Effects of varying wavelet bandwidth. In wavelet-based time-frequency analysis, there is an inherent trade-off between precision in the time and frequency domains (van Vugt, et al., 2007), so it is important to verify whether the effects observed during pre-stimulus time windows could be driven by post-stimulus activity. To address this issue, two separate analyses were performed to change the critical filter parameter: one with which we used a 3 wavelet bandwidth (cycles), and another in which we used 1 wavelet cycle to process the data, and both of these approaches to maximizing time resolution obtained the same effects as our reported results using 5.7 wavelet cycles. Figure S2 shows the results of the analyses using the 3 and 1 wavelet cycle approaches (and parallels the results of using 5.7 wavelet cycles, shown as Figure 2a in the manuscript). The results using 1, 3, and 5.7 wavelet cycles were each statistically significant after bootstrap correction for multiple comparisons (p<.05), and all showed a frontal pre-stimulus effect in the -150 to 0ms latency, whereas no significant differences in frontal theta were found between conditions in any post-stimulus latency (although post stimulus theta differences are reported for left parietal sites).

Simulations examining the effects of filter smearing on theta. We conducted simulations to determine the extent to which post-stimulus activity could contribute to a pre-stimulus effect (due to temporal imprecision of wavelet filtering). A 6 Hz sine wave beginning at 150ms post stimulus was generated, and the simulated data was analyzed using the same 5.7 cycle wavelet analysis that we had used to analyze the observed data (Figure S3). The post-stimulus theta simulation indicated that there was only limited amount of smearing prior to signal onset at 150ms post stimulus (Figure S3b, S3c), with only 24% of original real signal smeared into the pre-stimulus latency, and signal decay reaching full
width at half maximum (FWHM) at 6ms post-stimulus. This result was compared against results of a simulation of a pre-stimulus 6 Hz sine wave terminating at stimulus onset (Figure S3a, S3c). As shown in Fig. S4, the time course of the observed empirical difference in theta power between Item+Source and Item-Only trials closely paralleled the simulation of pre-stimulus theta and qualitatively differed from the post-stimulus simulation (Figure S3c, S3a). Thus, it is unlikely that the reported pre-stimulus theta effects were produced by filter blurring form the post stimulus latencies.
Supplemental Figures

**Fig. S1 Receiver Operating Characteristic (ROC) curve of item memory performance.** Proportion of item hits are plotted against the proportion of false alarms; chance performance is indicated by the diagonal line from the Cartesian origin to (1,1). Fitting the ROC to DPSD parameter estimates indicates a recollection value (Ro) of .52, and Familiarity estimate (d’) of 1.27.
Fig. S2. Topographic t-Statistic Maps of Significant Pre-Stimulus Differences in Theta between Item+ Source and Item Only Conditions from using different wavelet parameter analyses. Effects reported in the manuscript utilized 5.7 wavelet cycles (see Fig.2A, Fig.3A). Lowering wavelet cycles used increases resolution in the time domain at the expense of frequency resolution, demonstrating the absence of temporal smearing artifacts that could be due to wavelet filtering parameters. Color scale = Significant t-test values (p<.05), bootstrap corrected for multiple comparisons.
**Fig. S3** Results of Simulating Independent Pre-Stimulus and Post-Stimulus Theta to Assess Temporal Smearing Possibilities. A) Spectrogram of pre stimulus theta from -400ms to 0ms (stimulus onset) (top panel) simulated with a 6 Hz sin wave (bottom panel). Spectrogram color scale is in decibels of spectral power. Simulated theta signal processed with a 5.7 cycle wavelet analysis and image processed with a Hanning window applied for edge artifacts. B) Spectrogram of post stimulus theta increase at 150ms (top panel) simulated with a 6 Hz sin wave (bottom panel) [150ms post stimulus is where raw theta power peaks for all conditions of this experiment, i.e.: Fig. 2B and Fig 3B] ERSP signal decay is 76% by the pre-stimulus latency of -150ms to 0ms, with only 24% of original real signal smeared into the pre-stimulus latency, and signal decay reaching full width at half maximum (FWHM) at 6ms post-stimulus. Simulated theta signal processed with a 5.7 cycle wavelet analysis and image processed with a Hanning window applied for edge artifacts. C) Comparison of pre-stimulus and post-stimulus theta simulations with the actual data set reported. Bar graphs show theta power values in each 150ms latency before and after stimulus onset (0ms), proportional to the maximal theta power throughout the epoch. Simulating a post-stimulus increase in theta does not carryover into pre-stimulus latencies, while simulating pre-stimulus theta provides a nearly complete fit of the actual recorded data.
Chapter 3: Examining the Electrophysiology of Episodic Memory: ERP Evidence of Accurate Source Recognition without Recollection.

Abstract

Recollection is typically associated with high recognition confidence and accurate source memory. However, subjects sometimes make accurate source memory judgments even for items that are not confidently recognized, and it is not known whether these responses are based on recollection or some other memory process. In the current study, we measured event related potentials (ERPs) while subjects made item and source memory confidence judgments, in order to determine whether recollection supported accurate source recognition responses for items that were not confidently recognized. In line with previous studies, we found that recognition memory was associated with two ERP effects: an early on-setting FN400 effect, and a later parietal old-new effect [Late Positive Component (LPC)], which have been associated with familiarity and recollection, respectively. The FN400 increased gradually with item recognition confidence, whereas the LPC was only observed for highly confident recognition responses. The LPC was also related to source accuracy, but only for items that had received a high confidence item recognition response; accurate source judgments to items that were less confidently recognized did not exhibit the typical ERP correlate of recollection or familiarity, but rather showed a late negativity at frontal and right parietal sites. The results indicate accurate source judgments can occur even when recollection fails.
Introduction

Recognition memory judgments can be based on recollection of qualitative information about a previous event or on assessments of stimulus familiarity. Recollection and familiarity have been shown to be functionally dissociable and to rely on partially separable brain regions (for reviews see (Diana, et al., 2007; Eichenbaum, et al., 2007; Yonelinas, 2001a, 2001b; Yonelinas & Parks, 2007),(Yonelinas, et al., 2002). In addition, recollection and familiarity have been associated with distinct event related potential (ERP) modulations (Cansino & Trejo-Morales, 2008; Curran, 2000; Leynes, et al., 2005; Rugg & Curran, 2007; Wilding & Rugg, 1996; Yu & Rugg, 2010). That is, at time of retrieval, familiarity is associated with modulations of the FN400, an enhanced positivity for old items relative to new items observed from approximately 400-600ms post stimulus onset. The FN400 tends to have a mid-frontal scalp distribution which can extend to left and right frontal areas, plus central midline regions depending on which experimental materials are used (Friedman, 2000; Friedman & Johnson, 2000; M. J. Gruber & Otten, 2010; Rugg & Curran, 2007; Rugg, Mark, et al., 1998; Voss & Paller, 2007). In contrast, recollection has been linked with modulations of a positive going waveform that emerges approximately 600ms post stimulus and that is typically maximal over left parietal sites (Curran, 2000; Rugg, Mark, et al., 1998), and referred to as the Late Positive Component (LPC).

Dissociations between these ERP modulations have been reported based on subjective reports of recollection and familiarity (Duzel, et al., 1997), as well as correct and incorrect source memory discriminations (Wilding & Rugg, 1996), for review see (Rugg & Curran, 2007). In addition, the FN400 is found to increase gradually as a function of item recognition confidence whereas the LPC is limited to high confidence recognition responses (Woodruff,
et al., 2006; Yu & Rugg, 2010), consistent with cognitive models of the characteristics of familiarity and recollection (Yonelinas, 1999; Yonelinas, Aly, Wang, & Koen, 2010).

Although the distinction between recollection and familiarity is relatively well established, important debates remain about the functional nature of these processes and about how to best separate these processes (e.g., for a review see (Yonelinas, 1999, 2001a; Yonelinas, et al., 2010; Yonelinas & Levy, 2002). One approach is to use tests of source memory as measures of recollection (i.e., tasks that require subjects to retrieve where or how an item was studied), and compare this to performance on tests of item recognition (i.e., tasks that require subjects to discriminate between old and new items). The idea is that, if accurate source discriminations rely exclusively on recollection then performance on these tests can be used as an index of recollection. In contrast, if an item is recognized as old but leads to an incorrect source memory judgment this can be considered to provide a measure of familiarity. An alternative approach is to estimate recollection on the basis of recognition confidence judgments. The idea is that the recollection of qualitative information about a study event should lead to confident recognition memory responses, whereas familiarity in the absence of recollection should support lower confidence recognition responses. Thus in standard item recognition tests, recollection should be restricted primarily to high confidence recognition responses whereas familiarity should increase gradually across levels of confidence (see (Parks & Yonelinas, 2007, 2009; Yonelinas & Parks, 2007).

Usually, correct source judgments are associated with the highest level of recognition confidence, so these two approaches often lead to the same conclusions. However, subjects can sometimes recognize items with less than the highest level of item confidence, and yet go on to accurately determine the source of those items (e.g., (Quamme, Frederick, Kroll,
Yonelinas, & Dobbins, 2002; Wais, Squire, & Wixted, 2010; Yonelinas, 2001a; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001). What memory process might support these source discriminations is not yet clear. If they are based on recollection, one might expect that items associated with lower recognition confidence but correct source should be associated with an LPC modulation, but perhaps a somewhat smaller modulation than that seen for high confidence responses (Leynes & Phillips, 2008). In contrast, if they are based on familiarity (Diana, Van den Boom, Yonelinas, & Ranganath, 2011) or conceptual implicit memory (Paller, Voss, & Boehm, 2007), one might expect these trials to be associated with an ERP modulation resembling the FN400.

We sought to test these alternatives by examining the ERPs related to item recognition confidence and source memory judgments. We recorded ERPs during a recognition memory test in which subjects made old/new recognition judgments and source memory judgments (see Figure 1). Based on prior work, we expected to see an early fronto-central effect related to familiarity from 400-600ms (FN400) and a later left hemisphere effect related to recollection from 600-800ms (LPC). The FN400 effect was expected to increase gradually across item recognition confidence with increases in familiarity strength, whereas the LPC was expected to be restricted to the high confidence recognition responses. Moreover, we hypothesized that items leading to correct source memory judgments should produce a recollection effect compared to incorrect source judgments. Most importantly, we then examined the ERPs associated with correct source memory responses that were not recognized with the highest levels of recognition confidence. No prior study that we are aware of has examined this critical condition. If these items reflect the operation of
recollection then they should exhibit the late left hemisphere ERP signature consistent with recollection.

**Methods**

**Subjects & Stimuli:**

Twenty-five right-handed undergraduate students (eight males) were recruited from the University of California–Davis Psychology Department subject pool, and received credit for participation. Subjects were free from neurological, visual, motor, or other medical disorders, and the experiment was conducted as approved by the University of California – Davis IRB protocol for research on human subjects.

Word stimuli were selected from the Medical Research Council Psycholinguistics Database ([http://www.psych.rl.ac.uk/MRC_Psych_Db.html](http://www.psych.rl.ac.uk/MRC_Psych_Db.html)). Word stimuli had an average rating of concreteness of 589.50 (min=400, max=670), image-ability of 580.11 (min=424, max=667), Kucera-Francis Frequency of 30.38 (min=3, max =198), and an average number of 4.89 letters in each word (min=3, max=8). Stimuli were presented in uppercase letters in a white font (size 36), centered on a black background screen (Figure 1). Subjects were seated approximately 44 inches away from the screen.

**Procedure:**

During study, subjects encoded 200 words (presented in 4 lists of 50 words each) during an incidental encoding task. Two separate encoding tasks (i.e., ‘Animacy’ and ‘Manmade’ judgments), were used, which served as the basis for source memory decisions during retrieval (i.e., subjects made a yes/no responses to indicate if the item was alive, or to indicate if the item was manmade). These encoding tasks were selected to lead to
comparable levels of memory performance while allowing for reasonable levels of source
discriminability, i.e., (Ranganath, et al., 2004). The two encoding tasks were presented in a
blocked ABBA design, counterbalanced between subjects for the order of the two tasks.
Prior to each study block, subjects heard the instructions and there was a practice session of
10 stimuli that the experimenter and subject performed together in order to be sure that the
subject understood the task. None of the practice stimuli appeared in the test phase. After the
4 study blocks were presented there was a fifteen-minute filler task before the retrieval phase
of the experiment commenced.

During retrieval, the 200 stimuli presented during the encoding phase were randomly
intermixed with 100 new words (lures), for a total of 300 test stimuli (Figure 1). The test
stimuli were presented in 6 test blocks of 50 stimuli each. Prior to each stimulus
presentation, a fixation cross appeared in the middle of the screen for 650ms, during which
subjects were instructed not to blink, so as to minimize ocular artifacts in the EEG. The
retrieval probe then appeared on the screen for 1500ms, during which time the subject
viewed the stimuli, but were not yet cued to respond (Figure 1). Subjects were also
instructed not to blink while each stimulus was on the screen. After the 1500ms probe,
subjects were asked first to make an item recognition judgment followed by a source
recognition judgment; each of these responses was subject paced and therefore provided a
variable temporal jittering of each subsequent stimuli’s presentation. Prior to commencement
of the testing phase, subjects practiced on 10 sample trials with the experimenter present to
make sure they understood instructions and used the scale correctly.

For the item recognition judgment, subjects responded on a 5-point confidence scale, with
5 indicating that they were sure it was old, 4 indicating that it was probably old, 3 indicating
they were guessing, 2 indicating it was probably new, and 1 indicating they were sure it was new. For the source recognition judgment, subjects also responded on a 5-point scale with 5 indicating that they were sure it was from the animacy encoding task, 4 indicating that they thought it was from the animacy task but were not sure, 3 indicating they were guessing, 2 indicating that they thought it was from the manmade task but were not sure, and 1 indicating they were sure it was from the manmade task.

**EEG Acquisition and Analysis:**

EEG was recorded using a BioSemi ActiveTwo Recording System with a 32 channel electrode cap conforming to the standard International 10-20 System of electrode locations (Klem, Luders, Jasper, & Elger, 1999). Each subject was tested individually inside a sound-attenuating chamber. Stimulus presentation and behavioral response monitoring were controlled using Presentation software on a Windows PC. EEG was sampled at a rate of 1024hz. Subjects were instructed to minimize jaw and muscle tension, eye movements, and blinking. EOG was monitored in the horizontal direction and vertical direction, and this data was used to eliminate trials contaminated by blink, eye-movement, or other artifacts.

All EEG analyses were performed using custom Matlab code and functions from the EEGLab Toolbox for Matlab (Delorme & Makeig, 2004). Raw EEG data was re-referenced to averaged mastoids, downsampled to 256 Hz, and high-pass filtered at .1 Hz in order to optimize independent component analysis (ICA) decomposition for artifact correction. These data were epoched from 200 milliseconds before the onset of the retrieval item to 1.5 seconds following the retrieval item, and was baseline subtracted from -200 to 0 ms. Epochs containing single channel data which exceeded 4 standard deviations of the channel’s mean across epochs were removed to optimize ICA decomposition, as were epochs containing data
6 standard deviations from the pooled channel mean. This procedure was designed to remove primarily non-biological noise, while allowing stereotypical artifacts (such as eye-blinks) to remain. Data were then decomposed into temporally independent components using Infomax ICA (Bell & Sejnowski, 1995). Artifactual components (eye-blinks, muscle tension, etc) were manually identified and subtracted from the data and the artifact-corrected data were manually screened a second time to reject any remaining epochs with artifacts.

ERPs were averaged from the EEG data using ERPLAB software (http://erpinfo.org/erplab), a plug-in toolbox of Matlab functions for EEGLAB software (Delorme & Makeig, 2004). ERPs were grand averaged to a baseline of the 200ms preceding stimulus onset, using the un-weighted average of individual subjects’ trials. Mean amplitudes of latencies of interest for each condition were obtained, and analyzed in separate statistical software. A 30 Hz low pass filter was applied to grand average ERPs for data presentation, in order to filter out any remaining EMG or other high frequency noise in the averaged ERP waveforms. Mean amplitudes and statistics reported are of the raw ERP data, prior to low pass filtering.

We used a priori defined latencies of interest, based upon the established ERP literature of familiarity and recollection-related effects. Therefore, we focused our analysis on the time periods of 400-600 and 600-800ms, and our Old-New analysis (Figure 1) confirmed the detection of FN400 and LPC effects during these epochs in the current study. We report effects at the Cz and Cp5 electrode locations during the aforementioned epochs because this is where the voltage differences were most evident for the FN400 and LPC effects (results reported below, see Figure 1). For each ERP contrast we included subjects only if they had at least 13 artifact-free trials per condition (M. J. Gruber & Otten, 2010;
Otten, et al., 2006). For most of our contrasts, all subjects were included (N=25), and the average number of trials per condition was quite high (e.g., in the item confidence analysis an average number of trials per confidence level was of 37, 48, 26, 54, and 100 trials per subject). However, in cases in which it was necessary to exclude subjects, we report the sample size in the relevant result sections. When conducting ANOVA tests, results are reported after Greenhouse-Geisser corrections were performed.

Results

Behavioral Results:

Average response distributions of item memory confidence ratings for old and new items are displayed in Table 1. On average, recognition confidence ratings were higher for old items than for new items, t(24) = 21.58, p<.001, indicating that subjects were able to discriminate between old and new items. An examination of source memory responses indicated that .35 of the studied items were recognized with the highest level of confidence and received a correct source response (.15 and .20 led to low and high levels of source confidence, respectively), whereas .10 of the studied items were recognized with the second highest level of confidence and received a correct source response (.09 and .01 led to low and high levels of source confidence, respectively). Source memory accuracy was above chance (i.e., > 50 %) for both the low confidence item recognition trials (M=.58, SD=.15, t(24)=2.50, p = .02); reflecting the proportion of source correct divided by the sum of items receiving a source correct and source incorrect response) and the high confidence item recognition trials (M=.74, SD=.08, t(24) =14.35, p< .001). Thus subjects made accurate source memory responses for items that were recognized with both high and low levels of item recognition confidence.

Electrophysiological Results:
**Recognition Memory.** Item recognition was first examined by contrasting the ERPs associated with hits (old items receiving a 4 or 5 response) and correct-rejections (new items receiving a 1 or 2 response). Topographic maps of item recognition difference waves (Hits – Correct Rejections) for each 200ms time window of the recording epoch are shown in Figure 2A. ERPs for hits were more positive going that those for correct rejections (i.e., warmer colors on the topographical maps). This effect was apparent by approximately 400 ms after stimulus onset and was centrally distributed with a maximum over central midline electrode Cz (i.e.: FN400 effect), t(24) = 5.35, p < .001. However, between 600 and 800ms the FN400 effect diminished, and an LPC effect was observed that was maximal over left parietal electrode Cp5, t(24) = 3.73, p < .001. The ERPs observed at the Cz and Cp5 electrodes for the hits and correct rejections are plotted in Figure 2B and 2C, respectively. The early and late ERP differences correspond temporally and topographically to those identified in previous studies with the FN400 and the LPC, respectively (for reviews see [Curran, 2000; Friedman & Johnson, 2000; Rugg & Curran, 2007]). In addition, to control for potential differences in the confidence levels of the hits and correct rejections we examined performance for only the highest confidence responses (i.e., 1s and 5s), and this also led to the same pattern of FN400 and LPC effects. Thus, in our subsequent analyses, we used mean voltage amplitudes at electrode Cz from 400-600ms as a measure of the FN400, and at Cp5 from 600-800ms as a measure of the LPC.

**Item Memory Confidence.** To examine the relationship between the FN400 and LPC effects with the processes of familiarity and recollection, we plotted the average amplitude of the ERPs at each level of recognition confidence (collapsed across study status). Figs. 2D and 2E present results from an analysis which included the 14 subjects who had
more than 13 trials in each of the 5 response confidence bins (the same pattern was observed, however, when we included all subjects regardless of number of trials in each cell). As shown in Fig. 2D (see also supplementary Figure 1 for ERPs and topographic maps of each condition), the FN400 increased in a linear manner across confidence levels ($R^2 = .927$, $p < .001$), and introducing a quadratic component did not lead to a significant increase in variance accounted for ($F < 1$). In contrast, LPC amplitudes showed a non-linear U-shaped function across confidence levels (Fig. 2E, ERPs shown in Supplementary Figure 1) and introducing a quadratic component led to a significant increase in fit compared to a linear model ($R^2 = .994$, $F(1,2) = 272.56$, $p < .005$). Subsequent analysis indicated that an LPC effect was evident for confidently recognized items (i.e., ‘5’) compared to confidently rejected items (i.e., ‘1’) ($t(13) = 4.83$, $p < .001$), whereas the low confidence recognition responses (i.e.: ‘4’) were not different from the confidently rejected items (“1’s”), $t(13) = -.293$, $p = .77$. In contrast, FN400 amplitudes were more positive for both the high and low confidence recognition responses (see Figure 2D, Supplementary Figure 1) than for confidently rejected items (“1’s”), (i.e. $t(13) = 6.25$, $p < .001$, and $t(13) = 4.02$, $p = .001$ for high a low confidence responses, respectively)\(^1\).

Overall, the item recognition results are consistent with previous studies showing that recollection and familiarity are associated with topographically and temporally distinct ERP

\(^1\) Note that a further examination of Figure 2E indicated that the confident new responses (i.e., ‘1’ responses) were associated with a more positive going memory effect at CP5 during the 600-800 time window than the low confidence rejected items (i.e., ‘2’ responses). Although this difference was not statistically significant ($p<0.05$), we examined it further and found that it had a more posterior and later scalp distribution than the recollection-related response. This pattern of results has been reported before as dissociable from recollection, and been attributed to novelty-related processing and confidence (Woodruff et. al., 2006; Curran, 2004).
correlates (e.g., (Rugg & Curran, 2007; Woodruff, et al., 2006; Yu & Rugg, 2010), and with other studies indicating that familiarity increases gradually across item recognition confidence, whereas recollection contributes primarily to high confidence recognition responses (Yonelinas, 1997).

**Source Recognition.** ERPs were then examined to identify the correlates of recollection and familiarity on the basis of source discrimination. Thus, ERPs were examined for ‘source correct’ trials irrespective of the preceding item judgments (i.e., old items receiving a low or high confident correct source judgment), ‘source incorrect’ trials (i.e., old items receiving an incorrect source judgment or a ‘source unknown’ response) and ‘correct rejection’ trials (i.e., new items receiving a low or high confident new response). Compared to correct rejections, source correct trials should exhibit an LPC effect indicative of recollection, whereas the source incorrect trials should exhibit a reduced or non-evident LPC because recollection has presumably failed. In contrast, both source correct and source incorrect trials should be familiar and thus should exhibit the FN400 effect indicative of familiarity.

As expected, FN400 amplitudes were more positive for source incorrect trials than for correct rejections, \( t(24) = 3.05, \ p = .005 \), and also more positive going for correct source trials than for correct rejections, \( t(24) = 5.72, \ p < .001 \). FN400 amplitudes were higher for source correct trials than for the source incorrect trials as well, \( t(24) = 5.14, \ p < .001 \). An examination of the scalp topography of this effect indicated that it was maximal over central midline electrode Cz (Supplementary Figure 2D).

The amplitude of the LPC was significantly higher for source correct trials compared to incorrect source trials, \( t(24) = 5.603, \ p < .001 \) and compared to correct rejections, \( t(24) = \)
5.07, p<.001, whereas LPC amplitudes did not differ between the source incorrect trials and the correct rejections t(24) = .673, p=.50. Topographic maps contrasting the source correct and source incorrect trials to correct rejections showed that this effect exhibited a left lateralized effect (supplementary Figure 2B) for correct source memories, but no differences across the scalp for incorrect source judgments from 600-800ms.

**Source memory for low-confidence item hits.** The preceding analyses suggested that the LPC was specifically enhanced for items that received the highest confidence rating and/or items that were associated with accurate source decisions, which is consistent with a large body of evidence linking the LPC to recollection (Allan & Rugg, 1998; Allan, Wilding, & Rugg, 1998; Cansino & Trejo-Morales, 2008; Curran, 2000, 2004; Curran, DeBuse, & Leynes, 2007; Curran, et al., 2006; Curran & Doyle, 2011; Duarte, Ranganath, Winward, Hayward, & Knight, 2004; Duzel, et al., 1997; Friedman, 2000; Friedman & Johnson, 2000; Leynes, et al., 2005; Leynes & Phillips, 2008; Rugg & Curran, 2007; Rugg, Mark, et al., 1998; Rugg, Walla, et al., 1998; Rugg & Wilding, 2000b; Wilding, 2000; Wilding & Rugg, 1996; Woodruff, et al., 2006; Yu & Rugg, 2010). No significant LPC was seen for low confidence item hits, which might indicate that these items were not recollected. Our behavioral analyses, however, indicated that source memory accuracy was above chance for item hits that were recognized with low confidence. If recollection supported accurate source decisions for low confidence item hits, then it is possible that an LPC enhancement might be observed specifically for low confidence item hits that were also associated with correct source decisions. Alternatively, if familiarity supported accurate source decisions for low confidence hits, we would expect these trials to exhibit an increased FN400.
Figure 3 shows a series of topographic maps illustrating the time course for the amplitude difference between low confidence hit trials that were associated with correct source decisions and correct rejection trials. For comparison purposes, the time course of the difference between high confidence hits and correct rejections is also shown. Unlike the high confidence hits, which were associated with a significant increase of the FN400 and LPC (t(12)=.4.23, p=.001; t(12)=2.297, p=.04, respectively) (Figure 3A), low confident hits that were associated with correct source judgments exhibited no significant modulations for a positive difference from correct rejections, during either of the FN400 or LPC time windows (t(12)=.044, p=.965; t(12)=.45, p=.660, respectively). Instead, low confidence hits with correct source judgments were associated with more negative ERP amplitudes during these time windows (Fig 3B).

Thus, contrary to our initial predictions, low confidence item hits that were associated with correct source decisions exhibited neither the FN400 nor the LPC modulations that have been previously associated with familiarity or recollection, respectively. Instead, these trials were associated with more negative-going ERP amplitudes starting at approximately 600 ms post-stimulus. An exploratory ANOVA with electrode site and condition (low confidence item and source hit vs. correct rejection) was performed on representative electrode sites from four quadrants of the scalp (i.e., (Curran, et al., 2006; Woodruff, et al., 2006; Yu & Rugg, 2010): left frontal (F3), right frontal (F4), left parietal (P3), and right parietal (P4), during both the 600-800ms and 800-1000ms epochs. There was a significant effect of condition for both epochs, F(1,13) = 6.443, p=.026, F(1,13) = 14.309, p=.003, respectively, indicating that ERPs for low confidence recognition with accurate source memory were significantly more negative than ERPs of correct rejection trials during the 600-800ms time
and then extending into later epochs, with effects evident throughout the scalp, but emerging maximal at right parietal and left frontal regions.

**Discussion**

The current study examined the ERPs associated with item and source memory judgments. In line with previous studies we found evidence to suggest that two well known ERP modulations, the FN400 and the LPC, were differentially related to memory performance, as measured by recognition confidence and source memory accuracy. A third effect was also observed as a late, negative ERP for low confidence recognition with accurate source memory, which has not been reported in prior studies.

The FN400 increased linearly with item recognition confidence, whereas the LPC effect was restricted specifically for items that were recognized with the highest confidence responses. Moreover, for old items, the LPC was associated with correct, but not incorrect source memory judgments, whereas the FN400 was observed even for recognized items that were associated with incorrect source judgments. The FN400 and LPC results are consistent with previous ERP studies, neuroimaging studies (Kirwan et al., 2008; Montaldi, Spencer, Roberts, & Mayes, 2006; Ranganath, et al., 2004), as well as neuropsychological and behavioral studies (Bowles et al., 2007; Yonelinas, et al., 2002) that have shown that recollection supports high confidence item recognition responses, whereas familiarity strength increases gradually across levels of item confidence (Woodruff, et al., 2006; Yu & Rugg, 2010). The results are also consistent with previous studies showing that recollection supports the retrieval of qualitative source information (Duarte, et al., 2004; Guo, et al., 2006; M. K. Johnson, Verfaellie, & Dunlosky, 2008; Leynes & Phillips, 2008; Mitchell & Johnson, 2009; Rugg & Wilding, 2000a; Vilberg, Moosavi, & Rugg, 2006; Wilding, 2000;
Wilding & Rugg, 1996) and that familiarity can be observed even when the retrieval of source information fails (Curran, et al., 2006; M. K. Johnson, Kounios, & Nolde, 1997; R. Johnson, Jr., Kreiter, Zhu, & Russo, 1998; Mecklinger, Brunemann, & Kipp, 2011; Rugg, Mark, et al., 1998; Senkfor & Van Petten, 1998; Wilding, et al., 1995; Yovel & Paller, 2004), see (M. K. Johnson, Hashtroudi, & Lindsay, 1993; Yonelinas, 1999) for cognitive models of this).

The most critical new finding of the current study was related to the examination of the ERPs for low confidence item hits that were associated with correct source judgments. Unlike items that were recognized with high confidence, these trials did not exhibit modulations of the LPC. To the extent that the LPC effect indexes the recollection process (Allan & Rugg, 1998; Allan, et al., 1998; Leynes, et al., 2005; Rugg & Wilding, 2000b; Wilding, 2000); for reviews see (Curran, 2000; Eichenbaum, et al., 2007; Friedman & Johnson, 2000; Mecklinger, 2006; Rugg & Curran, 2007) the results indicate that accurate source recognition can occur even in the absence of recollection. One might argue that the lower confidence source correct items did not show an LPC simply because those responses included random guesses. However, subjects were given the opportunity to indicate that they did not know the study source (i.e., a source confidence of ‘3’), and these trials were not included in the analysis. Moreover, source accuracy for the low confident recognition items was above chance, indicating that some memory process must have supported these accurate source decisions. The lack of an LPC modulation for low confidence hits that were associated with correct source decisions also cannot be attributed to insufficient statistical power, because these trials were associated with a statistically significant negative going ERP effect during later latencies, which is the opposite of the LPC that was evident in the
recollection contrasts. More specifically, these trials were associated with a topographically widespread negative ERP modulation from 600ms post-stimulus (Fig. 3). This suggests that source recognition for low confidence hits was supported by a neurocognitive process distinct from recollection.

**What processes support accurate source memory in the absence of recognition confidence?** The process, or processes, that supported accurate source memory for lower confidence recognition trials in the current experiment is unclear, but there are several possibilities. One possibility is that accurate source memory for lower confidence recognition trials relied on familiarity. Several studies have shown that familiarity can support accurate source memory discriminations when recollection fails, e.g., (Diana, Yonelinas, & Ranganath, 2010; Quamme, et al., 2002), and that familiarity can be sensitive to contextual or source information (Tsivilis, Otten, & Rugg, 2001). For example, unitizing item and source information can lead to an increase in behavioral and ERP measures of familiarity (Bader, Mecklinger, Hoppstädter, & Meyer, 2010; Diana, et al., 2010; Wiegand, Bader, & Mecklinger, 2010). Although it is possible that familiarity supported accurate source decisions for low confidence hits, no significant N400 modulation was observed for these items, so there is little evidence to support this hypothesis.

A second, more speculative account of the late negativity that was related to source memory for lower confidence responses is that it reflects a form of ‘contextual familiarity’. The background for this idea is that episodic memories may reflect the binding of neural representations of item and context information (Diana, et al., 2007; Eichenbaum, et al., 2007). According to this view, item familiarity may reflect the strength of the item representation (e.g., a word) that supports recognition memory. Context information might
include information about the item (its meaning), as well as the place and time it was encountered, and how it was processed (see [Ranganath, 2010](#) for review). Recollection can be thought of as the recall of context information associated with an item, but it is possible that processing of a studied item could elicit weak activation of the associated context representation even when recollection fails. This type of contextual familiarity signal, in turn, could support source discrimination. This hypothesis, is admittedly post hoc - though some ERP evidence exists that distinguishes between effects of context and familiarity ([Ecker, Zimmer, & Groh-Bordin, 2007; Tsivilis, et al., 2001](#)) - so further studies that test this possibility will be necessary.²

The current study was not designed to discriminate between single and dual process recognition models, but the results join a growing number of ERP studies that provide support for the latter class of models ([Curran, 2000; Curran, et al., 2002; Diana, et al., 2006; Duzel, et al., 1999; Duzel, Vargha-Khadem, et al., 2001; Leynes, et al., 2005; Rugg & Curran, 2007; Woodruff, et al., 2006; Yu & Rugg, 2010](#)), in that recognition is composed of separable signals of recollection and familiarity, and provides initial evidence to suggest that there may be different forms of familiarity processing (item and context), consistent with what has been proposed in recent theories ([Diana, et al., 2007; Eichenbaum, et al., 2007; Ranganath, 2010](#)). The finding of two recognition memory ERP effects that were functionally dissociable shows that recognition cannot be accounted for by a single

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² Some source memory studies have shown a negative going memory effect (Late Parietal Negativity, ‘LPN’) ([Mecklinger et. al., 2007; Friedman et. al, 2005; Herron, 2007; Mecklinger et. al, 2003; Leynes & Phillips, 2008](#)) but it occurred at later latencies and at left parietal regions instead of the left frontal and right parietal regions we observed. In fact, as noted by [Johansson et. al., 2003](#), studies utilizing item judgments followed by source discriminations (i.e.: [Wilding, 2000; Duarte et. al, 2004; Trott et. al., 1999](#)) failed to find any LPN effect. Based on the different time course, topography, and conditions, it does not appear that the negative going ERPs in this experiment reflect the LPN.
underlying neural process. Moreover, these ERP effects were functionally dissociable with respect to how they varied across confidence, even when source accuracy was held constant. We know of no single process model of recognition that can account for these types of dissociations without postulating additional post hoc assumptions.

The current results have implications for how one goes about assessing the neural correlates of recollection and familiarity, and for current theories of recognition. For example, ERP and fMRI studies of recollection and familiarity are often conducted either by assessing recognition confidence or by contrasting source and item recognition judgments. The extent to which they have been successful at dissociating these processes suggests that they can provide a rough index of these processes, and these methods have largely led to converging results. However, a few studies that have used these methods have failed to find evidence for significant dissociations, e.g., (Gold et al., 2006; Wais, Wixted, Hopkins, & Squire, 2006). One potential account of these latter results then is that by assessing only item confidence or source recognition they did not successfully isolate recollection from familiarity. Given the relative simplicity of collecting item confidence and source confidence responses as we did in the current study, it would seem important to do so in future studies examining these processes, e.g., (Wais, et al., 2010).

The extent to which the current results generalize to other test procedures is currently unknown. However, the procedures that were used in the current experiment were chosen to reflect standard item confidence paradigms and standard source memory paradigms, so we expect the results to be quite general. Moreover, although recollection was found to lead to only the highest confidence recognition responses, other conditions would likely lead recollection to support a wider range of responses. For example, conditions in which subjects
are forced to respond using a confidence scale with many more levels of confidence should lead subjects to use a wider range of confidence responses for recollected items. Indeed, some evidence exists for graded ERP correlates of recollection (Leynes & Phillips, 2008; Vilberg, et al., 2006), consistent with the Source Monitoring Framework (SMF) and various dual process models of recognition, which contend that source monitoring can be supported by varying degrees of recollection (Hicks, Marsh, & Ritschel, 2002; M. K. Johnson, et al., 1993).

Conclusions

Recollection appears to support relatively high confidence item recognition responses, whereas familiarity based responses vary directly with item confidence. In addition, recollection supports accurate source recognition, whereas familiarity can be observed even when recollection of source information fails. However, accurate source recognition can occur even when recognition confidence is not high, and under these conditions it appears that accurate source recognition occurs in the absence of item recollection or familiarity.
**Tables & Figures**

<table>
<thead>
<tr>
<th>Recognition Confidence</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>.077</td>
<td>.245</td>
<td>.534</td>
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<td>.349</td>
<td>.146</td>
<td>.139</td>
<td>.039</td>
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</tbody>
</table>

**Table 1.0** Table 1. Average proportion of old and new items receiving each level of recognition confidence (1=sure new and 6=sure old).
Figure 1.0 Subjects made recognition memory judgments to a mixture of studied words and words that were new to the experiment. For each test item, subjects first made an item memory confidence judgment (i.e., is the item old or new to the experiment?), followed by a source memory confidence judgment (i.e., was the item encoded during the ‘animacy’ or ‘manmade’ conditions in the earlier study phase?). ERPs were recorded during the presentation of the test word, and classified according to the ensuing item and source memory responses.
**Figure 2.0 Recognition memory ERP effects.** Topographic maps of item recognition difference waves (Hits – Correct Rejections) for each 200ms latency window (A). Hits reflect old items leading to an item recognition response of 4 or 5, and correct rejections reflect new items leading to an item recognition response of 1 or 2. Mean ERPs for hits and correct rejections plotted for electrodes Cz and Cp5 (B and C, respectively). Mean ERP amplitude plotted as a function of item recognition confidence (collapsed across old and new items) for Cz and Cp5 effects (D and E, respectively). Mean ERP amplitudes for correct rejections, source incorrect and source correct trials for Cz and Cp5 (F and G, respectively).
Figure 3.0  Correct source memory ERPs for items receiving high and low items recognition confidence. (A) Time course of topographic maps of correct source judgments for high confident item hits (item 5), and (B) correct source judgments of low confident hits (item 4), each compared to correct rejections (new items receiving a 1 or 2 response) (Color scale = -2mV to 2mV). (C) ERPs at Cp5 during the 600-800ms latency.
**Supplemental Figures**

S1 Electrophysiological Correlates of Item Memory Confidence. Topographic maps of the item recognition confidence (N=25). ERPs at each confidence level are compared to the ERP for the items rated ‘new’ (i.e.: ‘1’ responses) during the early (A) and late (B) latency windows. C) ERPs for each level of confidence at Cz and CP5.
S2. Source Memory Effects. (A) ERPs at Cp5 for source correct, source incorrect and correct rejections (N=25). (B) Scalp topographies for the source correct vs. correct rejection, and the source incorrect vs. correct rejections at Cp5 during the later period (600-800ms). (C) ERPs at Cz for source correct, source incorrect and correct rejections. (D) Scalp topographies of correct and incorrect source memory effects at earlier latency of 400-600ms.
S3. Correct source memory ERPs for items receiving high and low items recognition confidence (N=25). (A) Time course of topographic maps of correct source judgments for high confident item hits (item5), and (B) correct source judgments of confident hits (item 4), each compared to correct rejections (new items receiving a 1 or 2 response) (Color scale = -2mV to 2mV). (C) ERPs at Cp5 during the 600-800ms latency.
Chapter 4: Neurophysiological evidence for selective recollection impairments in amnesia

Abstract

In several previous behavioral studies we have identified a group of amnestic patients that exhibit selective deficits in recollection with preserved familiarity-based recognition, but other behavioral studies have suggested that this type of patient might exhibit deficits in both recollection and familiarity. To examine recollection and familiarity processes in these patients, we recorded ERPs in three amnestic patients and six age matched controls while they made item recognition and source recognition judgments. ERP studies of recognition in healthy subjects have indicated that recollection and familiarity are related to a late positive component (LPC) and an earlier frontal component (FN400), respectively. The current patients were able to discriminate between old and new items, but were not significantly above chance at making source judgments. Moreover, whereas control subjects exhibited ERPs indicative of both recollection and familiarity, the patients only exhibited evidence of a familiarity correlate. The results verify that the patients do in fact exhibit a selective deficit in recollection.
Introduction

The study of amnesics with damage to the medial temporal lobes (MTL), such as patient HM (Scoville & Milner, 1957), has revealed that the MTL plays an essential role in long term episodic memory. However, contentious debate remains about whether amnesia impairs all, or just some forms, of episodic memory. On the one hand, there is evidence that patients can be identified who exhibit selective deficits in recollection (i.e., a process whereby qualitative information about prior episodes is retrieved), but exhibit normal familiarity (i.e., a process whereby studied items are judged to be more familiar than non-studied items) (Aly, Knight, & Yonelinas, 2010; Diana, Yonelinas, & Ranganath, 2008; Eichenbaum, et al., 2007; Montaldi & Mayes, 2011; Quamme, Yonelinas, & Norman, 2007; Quamme, Yonelinas, Widaman, Kroll, & Sauve, 2004; Simons, Dodson, Bell, & Schacter, 2004; Vann et al., 2009; Yonelinas, et al., 2004). However, other evidence suggests that amnesics always suffer from equivalent deficits in both recollection and familiarity, and that the MTL operates as a unified memory system critical for all forms of episodic memory (Amaral, Ishizuka, & Claiborne, 1990; Gold, et al., 2006; Manns, et al., 2003; Song, Wixted, Hopkins, & Squire, 2011; Squire, Zola-Morgan, & Chen, 1988; Squire & Zola, 1997; Wais, 2008; Wais, et al., 2006; Wixted & Squire, 2011).

One group of patients that has been described as exhibiting disproportional recollection impairments is a group of mild hypoxic patients (e.g., (Yonelinas, et al., 2004). Behavioral measures based on remember/know and receiver operating characteristic analysis of confidence judgments have converged in showing that those patients exhibit a deficit in recollection that leaves familiarity relatively or entirely intact (Aly, et al., 2010; Diana, et al., 2008; Quamme, et al., 2007; Quamme, et al., 2004; Simons, et al., 2004; Vann, et al., 2009).
However, there are two critical limitations to the studies that have been conducted with these patients. First, only behavioral measures of recollection and familiarity have been obtained. Claims about the fate of recollection and familiarity in these patients would be considerably strengthened if these processes were measured using independent physiological measures of recollection and familiarity. Second, the studies of recognition memory in these patients have been limited to remember/know (R/K) procedures whereby the subjects report on their subjective experience of the occurrence of recollection and familiarity, and to ROC studies based on recognition confidence responses made by the subjects. It has been suggested that amnesic patients might have difficulty understanding subjective report protocols (Baddeley, et al., 2001), thus it is critical to determine whether the deficits observed in these patients can be observed using measures that do not rely so heavily on subjective reports.

ERPs provide an ideal physiological measure of recollection and familiarity because there is a rich literature indicating distinct ERP correlates for these processes, which occur at separate times, have different topographic distributions on the scalp, and are differentially sensitive to conditions that modulate recollection and familiarity (for review see (Curran, 2000; Friedman & Johnson, 2000; Rugg & Curran, 2007; Rugg, Mark, et al., 1998), but also see (Paller, et al., 2007). Familiarity is associated with positive modulations of a negative peak from approximately 400-600ms and with mid-frontal scalp distribution, referred to as the FN400; whereas recollection has been found to elicit a Late Positive Component (LPC), a positivity observed between 600-800ms that is maximal over left parietal sites. ERPs have been successful in characterizing memory in patients with extensive medial temporal lobe damage (Lehmann, et al., 2007; Mecklinger, et al., 1998; Olichney, et al., 2000; Rugg, Roberts, Potter, Pickles, & Nagy, 1991; M. E. Smith & Halgren, 1989; M. E. Smith,
Stapleton, & Halgren, 1986), but only one prior study (Duzel, Vargha-Khadem, et al., 2001) has recorded memory-related ERPs when damage is less extensive and was found to be restricted to the hippocampus (Gadian, et al., 2000; Vargha-Khadem, et al., 1997), and this was limited as a case study of a single patient. While that patient with developmental hypoxic amnesia lacked an LPC, yet still maintained the FN400, it was not possible to interpret results beyond a generalized explicit memory deficit because recollection and familiarity were not explicitly measured.

Our empirical approach was to assess recollection and familiarity in amnesia using the LPC and FN400 as indirect measures of the memory retrieval processes. While scalp ERPs are unlikely to represent direct activity of medial temporal lobe regions largely thought to support these processes (Addante, et al., 2011; Luck, 2005; Niedermeyer & Lopes da Silva, 1982) (though see (Guderian & Duzel, 2005; Guderian, et al., 2009; Klimesch, et al., 2000) for plausible inferences, and (Duzel, Vargha-Khadem, et al., 2001; Fernandez, et al., 1999; Heit, et al., 1988; Rugg, et al., 1991; M. E. Smith & Halgren, 1989; M. E. Smith, et al., 1986) for empirical manipulations which suggest MTL regions are at least influential in their generation), they do represent neural activity related to the processing of recollection and familiarity based memories (Rugg & Curran, 2007). Since the debate concerning behavioral impairments of these patients (Montaldi & Mayes, 2011; Wixted & Squire, 2004, 2011; Yonelinas, et al., 2004) centers around whether or not they are impaired on the processes of recollection (Duzel, Vargha-Khadem, et al., 2001; Gold, et al., 2006; Manns, et al., 2003; Quamme, et al., 2004; Vann, et al., 2009; Yonelinas, et al., 1998; Yonelinas, et al., 2002) and/or familiarity (Song, Wixted, Hopkins, et al., 2011; Stark & Squire, 2003; Wixted & Squire, 2004), the LPC and FN400 measurements are particularly well suited to addressing
this. If the patients suffer from a selective deficit in recollection, we expect them to exhibit a reduced or absent LPC, but a normal FN400. If, on the other hand, the patients exhibit deficits in both processes, then both ERP effects should be reduced or unobservable. To the best of our knowledge no study has yet to collect simultaneous behavioral and physiological measured of recollection and familiarity in patients expected to have selective recollection impairments. Because source memory has rarely been assessed in studies of hypoxia, and specifically has not been conducted with the current patients, we used an item and source recognition paradigm to test episodic memory rather than relying on more subjective reports of recollection and familiarity such as the R/K procedure, which has been shown to be difficult for patients to understand (Gadian, et al., 2000; Vargha-Khadem, et al., 1997).

Using ERPs of both item memory confidence ratings and source memory measures, we found that mild hypoxia patients showed a reduced LPC, but maintained a normal FN400. These effects were mirrored by behavioral measures which indicated that the patients were at chance on the source recognition test but were above chance on the item recognition judgments. These results converge to demonstrate that these patients have a selective recollection deficit.

**Methods**

**Subjects**

Subjects included 3 patients and 6 matched controls. The experiment was conducted as approved by the University of California – Davis IRB protocol for research on human subjects, and subjects were paid for their participation. The patients were recruited at the UC Davis Medical Center. Controls were recruited from among hospital employees and volunteers, surrounding retirement communities, and patients’ spouses. Control subjects had
no history of neurological or psychiatric disease. The controls were matched to the patient
group for age, sex, years of education, and verbal IQ. Two of the patients (01 and 02) had
suffered a hypoxic episode resulting from cardiac arrest. These patients require a defibrillator
and thus were not able to undergo structural MRI scanning. Patient 03 acquired a relatively
circumscribed amnestic syndrome after recovering from a traumatic brain injury due to a car
accident. The latter patient received a clinical MR scan, and exhibited evidence of left > right
medial temporal lobe atrophy along with an area of white matter hyperintensity deep in the
left occipital lobe. Neuropsychological profiles of each patient are detailed below. Patient
01  age 40; scores on WMS-R (Verb./Vis./Gen./Att./Del) are as follows: 62/130/79/97/83;
score on WAIS-R IQ (Verb./Perf.) were as follows: [96 (full)]. Patient 02, age 42, scores on
WMS-R (Verb./Vis./Gen./Att./Del) are as follows: 94/77/87/96/80; score on WAIS-R IQ
(Verb./Perf.) were as follows: [94 (full)]. Patient 03, age 31, WMS-R
(Verb./Vis./Gen./Att./Del) (80/105/87/103/68), WAIS-R IQ (Verb./Perf.) [111 (full)].

Procedures

ERPs were recorded while subjects made item and source recognition memory
definitions. The stimuli were words selected from the Medical Research Council
Psycholinguistics Database (http://www.psych.rl.ac.uk/MRC_Psych_Db.html) with an average
rating of concreteness of 589.50 (min=400, max=670), image-ability of 580.11 (min=424,
max=667), Kucera-Francis Frequency of 30.38 (min=3, max =198) and an average number
of 4.89 letters in each word (min=3, max=8). Words were presented in uppercase letters in a
white font, size 36, centered on a black background screen (Figure 1). Subjects were seated
approximately 44 inches away from the screen.
Subjects first encoded 200 words (presented in 4 lists of 50 words each) during an incidental encoding task. Two separate encoding tasks (i.e., ‘Animacy’ and ‘Manmade’ judgments), were used, which served as the basis for source memory decisions during retrieval (i.e., subjects made a yes/no response to indicate if the item was alive, or to indicate if the item was manmade). These encoding tasks were selected to lead to comparable levels of memory performance while allowing for reasonable levels of source discriminability, (i.e., (Ranganath, et al., 2004), (R. Addante, C. Ranganath, & A. Yonelinas, Submitted). The two encoding tasks were presented in a blocked ABBA design, counterbalanced between subjects for the order of the two tasks. Prior to each study block, subjects heard the instructions and then received a practice session of 10 stimuli that the experimenter and subject performed together in order to be sure that the subject understood the task. None of the practice stimuli appeared in the test phase. After the 4 study blocks were presented, there was a delay of 90 minutes during which the electrode cap was applied before the retrieval phase of the experiment commenced.

During retrieval, the 200 stimuli presented during the encoding phase randomly intermixed with 100 new words (lures) (Figure 1) were presented in 6 test blocks of 50 stimuli each. To minimize ocular and motor artifacts, subjects were instructed not to blink or respond while each stimulus was on the screen. After the 1500ms probe, subjects then made an item recognition judgment followed by a source recognition judgment. Prior to commencement of the testing phase, subjects practiced on 10 sample trials with the experimenter present to make sure they understood instructions and used the response scale correctly.
For the item recognition judgment, subjects responded on a 5-point confidence scale, with 5 indicating that they were sure it was old, 4 indicating that it was probably old, 3 indicating they were guessing, 2 indicating it was probably new, and 1 indicating they were sure it was new (Figure 1). For the source memory judgment, subjects also responded on a 5-point scale with 5 indicating that they were sure it was from the animacy encoding task, 4 indicating that they thought it was from the animacy task but were not sure, 3 indicating they were guessing (i.e.: ‘source unknown’), 2 indicating that they thought it was from the manmade task but were not sure, and 1 indicating they were sure it was from the manmade task.

**EEG Acquisition and Analysis:**

EEG was recorded using a BioSemi ActiveTwo Recording System with a 32 channel electrode cap conforming to the standard International 10-20 System of electrode locations (Klem, et al., 1999). Each subject was tested individually inside a sound-attenuating chamber. Stimulus presentation and behavioral response monitoring were controlled using Presentation software on a Windows PC. EEG was sampled at a rate of 1024hz. Subjects were instructed to minimize jaw and muscle tension, eye movements, and blinking. EOG was monitored in the horizontal direction and vertical direction, and this data was used to eliminate trials contaminated by blink, eye-movement, or other artifacts.

All EEG analyses were performed using custom Matlab code and functions from the EEGLab Toolbox for Matlab (Delorme & Makeig, 2004). Raw EEG data was re-referenced to averaged mastoids, downsampled to 256 Hz, and high-pass filtered at .1 Hz in order to optimize independent component analysis (ICA) decomposition for artifact correction. These data were epoched from 200 milliseconds before the onset of the retrieval item to 1.5
seconds following the retrieval item, and was baseline subtracted from -200 to 0 ms. Epochs containing single channel data which exceeded 4 standard deviations of the channel’s mean across epochs were removed to optimize ICA decomposition, as were epochs containing data 6 standard deviations from the pooled channel mean. This procedure was designed to remove primarily non-biological noise, while allowing stereotypical artifacts (such as eye-blinks) to remain. Data were then decomposed into temporally independent components using Infomax ICA (Bell & Sejnowski, 1995). Artifactual components (eye-blinks, muscle tension, etc) were manually identified and subtracted from the data and the artifact-corrected data were manually screened a second time to reject any remaining epochs with artifacts. An average of 88% of ERP trials in patients were retained after artifact rejection (77%, 95%, & 91% for each of the 3 hypoxia patients, respectively), while on average 94% of ERP trials of controls were retained (95%, 91%, 97%, 91%, 97%, 93% for each of the 6 Controls, respectively).

ERPs were averaged from the EEG data using ERPLAB software (http://erpinfo.org/erplab), a plug-in toolbox of Matlab functions for EEGLAB software (Delorme & Makeig, 2004). ERPs were grand averaged to a baseline of the 200ms preceding stimulus onset, using the un-weighted average of individual subjects’ trials. Mean amplitudes of latencies of interest for each condition were obtained, and analyzed in SPSS software. A 30 Hz low pass filter was applied to grand average ERPs for data presentation, in order to filter out any remaining EMG or other high frequency noise in the averaged ERP waveforms. Mean amplitudes and statistics reported are of the raw ERP data, prior to low pass filtering.
For data analysis, we used apriori defined latencies of interest (Luck, 2005), based upon the established ERP literature of familiarity and recollection-related effects (Curran, 2000; Friedman & Johnson, 2000; Rugg & Curran, 2007) and prior work using the same paradigm (R. Addante, et al., Submitted). Therefore, we focused our initial analysis on the time periods of 400-600 and 600-800ms to assess our primary hypothesis concerning what the effect of mild hypoxia was on recognition memory processes. The established literature of ERP effects associated with recollection and familiarity-based processing also provided us with apriori defined regions of interest at which to assess effects during the aforementioned latencies, guiding our analysis to fronto-central electrode sites during the 400-600ms latency for familiarity-related ERPs, and to left parietal sites during the 600-800ms latency for recollection-related ERP activity. Subsequent analysis of an unexpected negative-going ERP effect from 800-1200ms was based on post-hoc time windows and electrode locations selected to best illustrate the nature of this new effect, consistent with a prior study (R. Addante, et al., Submitted). This latter approach was deemed appropriate for this exploratory analysis. For all of the reported analyses, all subjects had sufficient number of ERP trials to obtain effective signal-to-noise ratio (SNR) in ERP signals (i.e.: (M. J. Gruber & Otten, 2010; Kim, Vallesi, Picton, & Tulving, 2009; Otten, et al., 2006; Zola-Morgan, Squire, & Amaral, 1989).

Signal-to-noise ratio (SNR) is an issue of any ERP experiment, especially of clinical patient populations in which it can be particularly difficult to obtain clean EEG signals (Luck, 2005), and our availability of only an average of 50 and 62 available trials per patient for conditions of low confident hits and high confident hits, respectively, was a SNR challenge from the several hundred trials used in the extant ERP study of retrieval in mild
amnesia, i.e.: (Duzel, Vargha-Khadem, et al., 2001). Yet, visual inspection of ERPs (i.e.: Figs.4, 5, & 6) reveals remarkably clean signals, and the points noted in the discussion section concerning power issues also speak to the validity of the effects in terms of SNR limitations. EEG data at a single electrode channel is typically too noisy for obtaining significant effects and must be combined with other separate electrode sites in most studies, though it is preferable to interpret results of data in its most unadulterated form. The clean ERP signals observable in Figures 4, 5, & 6 is therefore strengthened by the fact that our effects were obtained at the single electrode level, without resorting to the common practice of collapsing across several electrodes, i.e.: (Curran, et al., 2006; Woodruff, et al., 2006; Yu & Rugg, 2010), which is practice commonly done to obtain effective SNR of ERPs for statistical significance.

**Results**

**Behavior**

*Item recognition.* The item recognition confidence ratings for old and new items are presented in Table 1. Recognition performance (Figure 2) was first assessed by subtracting the false alarm rate (i.e., the proportion of 4 and 5 responses to new items) from the hit rate (i.e., the proportion of 4 and 5 responses to old items). Note that the same pattern of results was observed when d’ values were assessed. As expected, the patients were significantly impaired at item recognition when compared to controls (t(7) = 2.96, p = .022). None the less, the patients still performed item recognition at significantly above chance levels, t(2) = 3.49, p = .036 (one tailed), suggesting that they exhibited some preserved item recognition ability.
Closer inspection of the high and low confidence recognition responses (Table 1) indicated that the recognition memory impairment seen in the patients was due exclusively to a reduction in high confidence recognition responses. That is, for the low confidence recognition responses the patients and controls accepted the same number of old items (M=.29 for both the patients and controls), and new items (M=.21 and .20 for the patients and controls respectively). In contrast, for the high confidence recognition responses the patients produce fewer responses to old items than did the controls (.50 vs. .35, t(7) = -1.148, p=.095, one-tailed), and slightly more high confidence false alarms to new items (.12 vs. .06). While differences in raw response trials was limited by low numbers of subjects, when comparing accuracy of high confidence recognition responses between groups (i.e., hits minus false alarms), high confidence recognition was significantly reduced in the patients compared to controls (t(7) = 2.49, p=.04). Given that recollection is expected to support high confident recognition responses, the results suggest that the patients exhibited a deficit in recollection rather than familiarity. To assess this possibility further, the average confidence data in Table 1 was fit to the dual process signal detection model (Yonelinas, 1994). The model indicated that recollection was reduced in the patients (R=.01) compared to the controls (R=.31), whereas familiarity estimates were similar (d’ = .78 and 1.12 for the patients and controls, respectively). However, when the model was fit to individual subject Receiver Operating Characteristic Curves (ROCs), the differences between patient and control estimates were not significant (p’s > .05). Thus the behavioral evidence from item recognition confidence responses for a deficit in recollection can only be taken as suggestive. More direct evidence of a recollection deficit, however, was seen in the source recognition responses.
Source recognition. Source recognition confidence ratings for old items are presented in Table 2. Source recognition performance (Figure 2) was assessed by subtracting the false alarm rate (i.e., the proportion of high and low confidence source incorrect responses) from the hit rate (i.e., the proportion of high and low confidence source correct responses). As expected, the patients were significantly impaired at source memory accuracy compared to the controls (t(7) =2.55, p = .037). In addition, source accuracy in the controls was significantly above chance (t(5) =6.57, p = .001) whereas the patients were not above chance (t(2) = .822, p = .497). An examination of the high and low confidence source correct responses (Table 2) indicated that the source memory impairment was restricted primarily to the high confidence responses. That is, the proportions of low confidence correct source responses were .24 and .22 for controls and patients, respectively (t(7)= .29, p=.78), whereas the high confidence responses were, .25 and .03, (t(7) = -2.54, p=.038). To the extent that source recognition relies heavily on recollection, the results indicate that the patients exhibited a pronounced recollection deficit.

Electrophysiology

Item Recognition Memory. Item recognition ERPs were examined by contrasting the ERPs associated with low and high confidence recognition responses (i.e., 4 and 5 responses) to old items. These response bins were selected because they contained a sufficient number of responses for each patient and control (after artifact rejection there were a mean number of 50 and 62 trials in these respective bins for patients, and the minimum number for any patient was 41 trials), and they were expected to reveal effects related to both recollection and familiarity. That is, high confidence responses are expected to contain more recollected items than low confidence responses and also be more familiar than the low confidence responses.
Figure 3 presents the topographies of the item recognition memory effects (i.e., high minus low confidence responses) from the time of stimulus onset to 1400ms, broken into 200ms time bins. The figure illustrates that for the control subjects the ERPs for confidently recognized items were more positive than for low confidence items (i.e., warmer colors). This effect began approximately 400 ms post-stimulus onset with a broad fronto-central distribution which then gradually shifted to exhibit a left posterior distribution by 800-1000 ms. This pattern of results is consistent with a large body of literature that has revealed an early FN400 associated with familiarity and a later LPC related to recollection, e.g., (Curran, 2000; Friedman & Johnson, 2000; Rugg & Curran, 2007; Rugg, Mark, et al., 1998). Most importantly, for the patients there was also evidence of an enhanced central positivity between 400-600 ms, which then quickly dissipated, leaving little evidence of a later left posterior shift, as was seen in the normal group i.e.: (Duzel, Vargha-Khadem, et al., 2001; Mecklinger, et al., 1998).

To further quantify the ERP effects related to recollection and familiarity, we focused on the FN400 by examining electrode FC1 during the 400-600ms window, and the LPC by examining electrode P3 during the 600-800ms window. The time windows were selected based on prior studies, e.g.: (R. Addante, et al., Submitted), for reviews see (Curran, 2000; Friedman & Johnson, 2000; Rugg & Curran, 2007; Rugg, Mark, et al., 1998). The specific electrodes analyzed were selected because the observed memory effects were maximal in these channels. Figure 4 shows the ERPs for high and low confidence recognition trials for the patients and controls at electrode sites FC1 and P3. We conducted a 2x2 mixed model ANOVA, using group (patients vs. controls) as a between subjects factor and confidence (high vs. low) as a within subjects factor, for the FN400 amplitude (i.e., FC1 from 400-
600ms) and a similar analysis for the LPC amplitude (measured at electrode P3 from 600-800). For the FN400, there was a main effect of confidence $F(1,7)=5.76$, $p=.047$, indicating that the high confidence responses were more positive going than the low confidence responses. Importantly there was no evidence of a confidence by group interaction, $(F(1,7) < 1)$, indicating that the FN400 did not differ across patients and controls. In contrast, for the LPC there was a main effect of confidence, $F(1,7)=5.75$, $p=.048$, but this was qualified by a significant confidence by group interaction, $F(1,7) = 7.58$, $p=.028$. Subsequent analyses indicated that this interaction arose because only the control subjects exhibited a significant LPC $(t(5)=8.28$, $p=.0004)$, whereas there was no evidence of this effect in the patients $(t(2)=-.129$, $p=.908)$.

To quantify the differential group effect on the FN400 and the LPC, these memory ERPs (i.e., the ERP magnitude for the high-confidence “5” responses were subtracted from that of the low confidence “4” responses) were examined in each group (Figure 4). A 2x2 ANOVA indicated that there was a significant interaction between group (patient vs. controls) and ERP effect (FN400 and LPC) showing that the LPC was preferentially disrupted in the patients $F(1,7)=21.14$, $p=.002$. The relationship between patients and controls for FN400 and LPC effects is shown graphically in the bottom right panel of Figure 3. These results suggest that the patients were making accurate high confidence recognition judgments based upon intact familiarity, but showed no detectable evidence of recollection-related brain activity during item recognition. It should also be noted that when patients responded that an item was “old” with High-confidence, there was a greater than 3-fold chance of an error compared to normal controls (i.e. ~15% were actually new words, compared to <5% in controls, see Table 1).
The failure to find an LPC in the patients might be related to insufficient power, particularly given there were only three patients. To assess this a Bayes Factor analysis (Rouder, Speckman, Sun, Morey, & Iverson, 2009), c.f.: (Zhang & Luck, 2011) was conducted and revealed that in comparing high and low confidence recognition ERPs for patients at P3 from 600-800ms, it was 2.66 times more likely that the null hypothesis is true than the possibility that the alternative hypothesis is true (i.e., that there was a significant LPC in this group), meaning that it is 2.66 times more likely that there is no recollection related LPC effect in the amnestic patients than there is the chance of a real ERP difference related to recollection which went undetected. Additionally, in comparing group differences in the FN400 effect between patients and controls, the Bayes Factor was 2.34, which reveals that it is 2.34 times more likely that there are no differences in familiarity-related activity between patients and controls, and thus that familiarity is unaffected in the patients. These results confer further statistical evidence that the patients do exhibit a selective deficit in recollection rather than familiarity.

Source Memory. Source recognition ERPs were examined by contrasting the ERPs associated with source correct trials (i.e., old items leading to high or low confidence correct source responses) with old items that did not receive a correct source response (i.e., old items that received either a source incorrect or a source unknown response)\(^3\). After artifact rejection there were a mean number of 43 and 132 trials in each of these two bins, and the

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\(^3\) Note that we included the source unknown trials with the source incorrect trials to be consistent with prior studies that have not given subjects the opportunity to indicate a guess response, and because it increased the number of responses in our source ERP contrast. None the less, we also conducted a subsequent analysis in which we excluded the source unknown trials from the analyses and found that this resulted in the same pattern of results.
minimum number for any subject was 37. This contrast was expected to provide a measure of recollection.

Figure 5 shows the topographies of the source memory effects in the controls and patients across the recording epoch. For the Controls, the source correct trials produced a more positive going ERP than the source incorrect trials, which was maximal over left posterior regions from 600-800ms – a signal indicative of recollection. In contrast, for the Patients no such memory effect was observed. In fact, there was evidence for a very late negative going effect centered over right posterior regions instead. ERPs of source correct and source incorrect responses at P3 are shown in Figure 5. A 2x2 ANOVA examining the LPC failed to reach a level of significance at electrode P3, likely due to low power (F(1,7)=2.06, p=.194 for main effect of condition; F(1,7) = 2.164, p= .185 for condition x group interaction), but note that at the adjacent left parietal electrode Cp5 (which was the site of maximal activation in a prior study using the identical paradigm ), a 2x2 ANOVA did reveal a significant condition x group interaction, F(1,7)=9.27, p=.019.

Follow up planned t-tests were performed on the P3 electrode, and indicated that there was a significant of source memory on the LPC in controls, t(5)=2.34, p=.03 (one tailed), but not in patients (t(2)= -.027, p=.49). The same results were found in source memory comparisons when controlling for the preceding item memory strength, i.e., (Wais, et al., 2010). The Bayes Factor for the difference in source memory ERPs at P3 from 600-800ms in Patients was 2.68, which suggests that it is far more likely that the null hypothesis (i.e.: that there are no differences in patients’ ERPs for correct and incorrect source memory responses) is true, than it is that the alternative hypothesis of a significant LPC effect in the patients is true. Thus, the patients were selectively impaired in recollection as measured by
source memory ERPs as well. Source correct ERPs were also more positive going than source incorrect ERPs during the FN400 latency of 400-600ms at fronto-central sites for both patients and controls, but this difference was not significant.

In epochs following the LPC, the patients exhibited a prominent negative-going ERP effect that was maximum over left frontal and right parietal sites (F7 and P4) during the 800-1000ms and 1000-1200ms period for accurate source memory judgments that was not seen in the controls (Figures 5 and 6). This effect was not predicted in this experiment, but we report several post hoc analyses to quantify this potentially interesting effect further. We conducted a 2x2 ANOVA to assess the relationships between ERPs for source correct and source incorrect conditions at representative left frontal and right parietal electrode sites (F7 and P4, respectively), between Patient and Control groups. There was a main effect of electrode (F(1,7) = 5.17, p=.05), as well as a main effect of condition (F(1,7) = 5.85, p=.046), plus a significant condition x group interaction (F(1,7) = 11.695, p=.011); electrode did not interact with any other factors. Thus, source memory effects were the same across left frontal and right parietal electrodes, but the source memory effects were different between patients and controls at both electrode sites. Follow-up comparisons were conducted to determine the factors underlying the condition x group interaction. In the patients, correct source memory responses elicited ERPs that were significantly more negative going than incorrect source memory responses at both right parietal (P4) and left frontal (F7) regions of the scalp, t(2) = 6.16, p=.025, t(2) = 4.42, p=.047, respectively. There were no significant differences in Controls for source memory from 1000-1200ms at either left frontal, t(5) = .66, p=.53, or right parietal electrode sites, t(5) = .32, p=.72.
**Discussion**

The current experiment examined ERPs related to item and source recognition memory judgments in order to examine the role of recollection and familiarity processes in three amnesic patients. In line with prior studies indicating that these patients have a selective deficit in recollection, e.g., (Aly, et al., 2010; Diana, et al., 2008; Quamme, et al., 2007; Quamme, et al., 2004; Simons, et al., 2004; Vann, et al., 2009), the current behavioral results indicated that the patients were severely impaired at source recognition (i.e., were impaired relative to controls, and did not perform significantly above chance). Item recognition was also impaired, but performance remained above chance, indicating some preserved item recognition ability. In addition, an examination of recognition confidence responses indicated that the patients’ item recognition impairments were due entirely to a reduction in high confidence recognition responses. Since recollection generally supports high confidence recognition responses (R. J. Addante, C. Ranganath, & A. P. Yonelinas, Submitted; Bowles, et al., 2007; Ranganath, et al., 2004; Woodruff, et al., 2006; Yu & Rugg, 2010), the results provide further evidence that the patients suffered a selective recollection deficit. Prior studies with these patients have used subjective report methods and ROC methods to measure recollection (Quamme, et al., 2004; Vann, et al., 2009; Yonelinas, et al., 2002; Yonelinas, et al., 2004). The current results extend those results to a source recognition paradigm allowing us to verify that their recollection deficits were not limited to abnormalities in subjective reports, but rather generalized, with significant impairment of item recognition and severe impairment in the ability to retrieve accurate source information.

The ERP results were largely as hypothesized, and support a selective deficit in recollection. That is, in the controls, we identified the FN400 and the LPC components that
have been associated with familiarity and recollection, respectively (Curran, 2000; Friedman & Johnson, 2000; Rugg & Curran, 2007). The FN400 was observed in the item recognition confidence contrast, whereas the LPC was observed in both the item recognition and the source memory contrasts. Importantly, the familiarity correlate (FN400) was normal in the patients whereas there was no evidence of the recollection correlate (left parietal LPC), even as a graded signal (Leynes & Phillips, 2008; Vilberg, et al., 2006). The ERP results join two previous studies which have indicated that hypoxic amnesics (Mecklinger, et al., 1998) and a hypoxic patient with selective hippocampal damage (Duzel, Vargha-Khadem, et al., 2001) each show selective reductions in the LPC, while leaving an earlier mid-frontal ERP component intact. However, neither of those earlier studies were designed to assess recollection and familiarity behaviorally (they included only yes/no item recognition measures), so it was not clear whether those patients exhibited behavioral deficits consistent with their ERP deficits. Thus, the current study is the first to firmly link the ERP reductions to recollection deficits.

The current results support dual process models of recognition memory (Yonelinas, 1994, 1999; Yonelinas, et al., 2010; Yonelinas, Dobbins, Szymanski, Dhaliwal, & King, 1996; Yonelinas & Parks, 2007) which assume that recollection and familiarity reflect distinct memory processes, and are problematic for single process models that treat familiarity as simply a weak form of recollection (W. Donaldson, 1996; Dunn, 2004; Wixted & Mickes, 2010). That is, the temporal and topographical differences in the ERP correlates of recollection and familiarity indicate that they must involve at least partially different underlying neural generators (Friedman & Johnson, 2000; Rugg & Curran, 2007). In contrast, had we found that the familiarity effects were simply a weaker version of the
reollection-related ERP, this would have provided support for the single process accounts. Evidence that the LPC and FN400 are dissociable memory effects, and not merely correlates of memory strength, has been further demonstrated in research showing an intact LPC but no FN400 in aging populations (T. H. Wang, de Chastelaine, Minton, & Rugg, 2011), making it difficult to attribute our observed ERP differences as due to a gradient of memory strength.

The current results do not speak directly to questions of which brain structures were involved in recollection and familiarity because scalp ERPs do not allow us to determine with any precision the neural generators of the observed ERPs (Luck, 2005; Niedermeyer & Lopes da Silva, 1982), and lesion location (likely microscopic) could not be verified by MRI in the two hypoxic patients because of pacemakers. However, there is indirect evidence that the recollection deficits we observed likely did arise as a consequence of damage to medial temporal lobe structures, especially hypoxia-sensitive sectors of the hippocampus (Di Paola, et al., 2008; Hopkins, Kesner, & Goldstein, 1995a, 1995b; Rempel-Clower, Zola, Squire, & Amaral, 1996; Zola-Morgan, et al., 1986). First, single unit potentials recorded within the medial temporal lobe have identified two memory related components that are similar in time course to scalp recorded potentials we observed (Farovik, et al., 2008; Fernandez, et al., 1999), (Heit, et al., 1988), and cortical ERPs similar to those which we observed (i.e.: P300) have been attributed to medial temporal lobe regions (Klimesch, et al., 2000; Rugg, et al., 1991; M. E. Smith & Halgren, 1989; M. E. Smith, et al., 1986), likely due to cortico-hippocampal re-entrant loops, c.f. (Miller, 1991), [for similar interpretations of effects see: (Guderian & Duzel, 2005; Guderian, et al., 2009)]. Additionally, there is extensive anatomical (Lavenex, Suzuki, & Amaral, 2004; Saleem, et al., 2008; Suzuki & Amaral, 2004) and functional (Diana, et al., 2007; Fernandez & Tendolkar, 2006; Kahn, et al., 2008;
Ranganath, et al., 2005; Takahashi, et al., 2008) connectivity between the medial temporal lobe regions thought to differentially support recollection and familiarity (i.e., hippocampus & perirhinal cortex)(Eichenbaum, et al., 2007), and the cortical regions where associated ERP effects manifest at the scalp (i.e., lateral parietal cortex & medial frontal cortex) (Lavenex, et al., 2004; Suzuki & Amaral, 2004; Vilberg & Rugg, 2008), respectively, which provides the primary connectivity pathways of MTL-cortico networks for memory (Miller, 1991; Simons & Spiers, 2003). Second, although severe hypoxia can be associated with damage outside the hippocampus, a robust relationship between mild hypoxia and hippocampal damage has been established from volumetric and histological studies (Cummings, Tomiyasu, Read, & Benson, 1984; Di Paola, et al., 2008; Duzel, Vargha-Khadem, et al., 2001; Hopkins, et al., 1995a, 1995b; Kartsounis, Rudge, & Stevens, 1995; Mecklinger, et al., 1998; Press, Amaral, & Squire, 1989; Reed & Squire, 1997; Rempel-Clower, et al., 1996; Squire, Amaral, & Press, 1990; Squire, Amaral, Zola-Morgan, Kritchevsky, & Press, 1989; Yonelinas, et al., 2002; Zola-Morgan, et al., 1986), discussed in(Yonelinas, et al., 2002; Yonelinas, et al., 2004). 

High resolution MRI and postmortem examination of mild hypoxics often reveals no sign of parahippocampal or temporal lobe atrophy even when hippocampal volumes are reduced by 50% (Rempel-Clower, et al., 1996; Squire, et al., 1990). Voxel Based Morphometry has revealed that “Patients with hypoxic amnesia may present damage in other brain regions, but only hippocampal atrophy is common in all of them” (Di Paola, et al., 2008) (p.719. In addition, the selective recollection deficits observed in the current patients as measured using the ROC method (Yonelinas, 1997; Yonelinas & Parks, 2007) are similar to those observed in rats with selective hippocampal lesions using similar ROCs methods (Eichenbaum, Sauvage, Fortin, &
Yonelinas, 2008; Eichenbaum, et al., 2007; Fortin, et al., 2004; Sauvage, et al., 2008). Thus, taken together with existing literature, the results are in good agreement with recent models of the medial temporal lobe (MTL) which propose that the hippocampus is particularly important in supporting recollection (Diana, et al., 2007; Eichenbaum, et al., 2007) and that the surrounding cortex is sufficient for familiarity4.

This study, like many neuropsychological patient studies, is limited by small sample size, and recruiting mild hypoxia subjects from cardiac arrest (e.g., patient RB, (Zola-Morgan, et al., 1986) is particularly challenging (i.e.: (Di Paola, et al., 2008), p.726). The current study included all the chronic well-circumscribed amnesia patients currently available; and despite power limitations, we obtained significant group effects in analyses of both item and source memory contrasts, and which underscore the magnitude of both the ERP effects and amnesic deficits. A Bayes Factor analysis suggested it is unlikely that the null LPC effects of patients, and the result of no between-group differences in the FN400, was due to low power, and post-hoc analyses of Controls using randomized configurations of matched sample size (N=3) revealed significant LPC effects. Another limitation of the current study is that it was not possible to obtain MRI measures of the hippocampus in the cardiac arrest patients (GH & RM), due to their defibrillators. Structural MRI was available for the post-traumatic amnesia patient DB, which indicated left > right hemisphere MTL atrophy as well as a left occipital lobe white matter hyperintensity. Thus, the precise extent

4The finding that the current patients exhibited a selective deficit in high confidence item recognition responses is a stark contrast to the response pattern of a patient with a selective perirhinal cortex lesion that left the hippocampus intact (patient NB, Bowles et. al., 2007). The latter patient showed a reduction in low confidence responses but normal levels of high confidence recognition responses. This neuropsychological dissociation of memory confidence between patients is consistent with predictions of these models, while particularly problematic for alternative models that propose a shared processing of recollection and familiarity gradients across MTL regions (i.e.: Squire et. al., 2007; Squire, 2004; Squire & Zola, 1997).
of hippocampal damage in these patients is currently unknown, the likelihood of all 3
patients having hippocampal lesions is very high based on multiple published patient studies
(Cummings, et al., 1984; Di Paola, et al., 2008; Duzel, Vargha-Khadem, et al., 2001;
Hopkins, et al., 1995a, 1995b; Mecklinger, et al., 1998; Press, et al., 1989; Rempel-Clower,
et al., 1996; Squire, et al., 1990; Squire, et al., 1989; Yonelinas, et al., 2002; Zola-Morgan, et
al., 1986) with detailed MRI and/or neuropathological results available.

The literature linking the LPC to recollection is well established (Curran, 2000;
Curran & Doyle, 2011; Friedman & Johnson, 2000; Rugg & Curran, 2007; Rugg, Mark, et
al., 1998); the link between familiarity and the FN400 is also robust (Curran, 2000; Friedman
& Johnson, 2000; Rugg & Curran, 2007), but this effect is associated with other processing
as well. Some findings have suggested that the FN400 may also be a correlate of conceptual
priming (Paller, et al., 2007; Voss & Federmeier, 2011), particularly for non-word stimuli
(Curran & Hancock, 2007; D. I. Donaldson & Curran, 2007). The current study utilized
verbal materials rather than faces, so it is not clear how relevant those studies are to the
current results, and the relationship of the FN400 to familiarity has been consistently upheld
(Groh-Bordin, Zimmer, & Ecker, 2006; Stenberg, Hellman, Johansson, & Rosen, 2009;
Stenberg, Johansson, Hellman, & Rosen, 2010). However, it is possible that the current
patients might also show a preserved FN400 on conceptual implicit memory tests. In fact,
amnesic patients generally do exhibit normal conceptual priming (Levy, Stark, & Squire,
2004) as well as normal familiarity-based recognition (Gold, et al., 2006; Quamme, et al.,
2004; Vann, et al., 2009; Yonelinas, et al., 2001; Yonelinas, et al., 2002) whereas patients
with documented damage to the perirhinal cortex show impairments in both familiarity and
conceptual implicit memory (Bowles, et al., 2007; W. C. Wang, Lazzara, Ranganath, Knight, & Yonelinas, 2010; Yonelinas, et al., 2002).

One unexpected finding in the current study was that the patients exhibited a significant negative going ERP effect from 800-1200ms in the source correct vs. source incorrect contrast, which was not observed in the control subjects. A similar pattern of negative going ERPs for accurate source judgments was seen in a recent study of healthy subjects (R. Addante, et al., Submitted). In that study, high confidence source judgments were associated with an LPC, whereas low confidence source judgments showed a later negativity (see Figure 3 & Supplemental Figure 3 of the preceding Chapter 3). A post-hoc analysis of the ERPs in the current healthy control group also revealed a negative going ERP related to low confidence item judgments with source correct responses (Supplemental Figure 1). The functional significance of this effect is unclear. One possibility is that it may reflect the neural processing associated with ‘contextual familiarity’, separable from item familiarity and recollection. Consistent with the Binding of items and context (BIC) model of the MTL (Diana, et al., 2007; Eichenbaum, et al., 2007), context familiarity would be supported by the parahippocampus (with item familiarity supported by perirhinal cortex), and some source judgments might be made by retrieval of context information, without dependence upon either recollection or the hippocampus. A prediction for future testing is that patients with selective perirhinal lesions, e.g., patient NB, (Bowles, et al., 2007) may uniquely demonstrate impaired item familiarity but preserved context familiarity if tested appropriately for context information independent from item information, though this possibility would admittedly be a challenge to empirically isolate, and may be better suited
for studies of more controlled lesions in rodents, using paradigms that have been shown to
differentiate recollection from familiarity, i.e.: (Fortin, et al., 2004; Sauvage, et al., 2008)

Conclusions

The ERP demonstration of recollection deficits with preserved familiarity in human
patients parallels the results from controlled animal lesion studies of the hippocampus
(Fortin, et al., 2004; Sauvage, et al., 2008) and confirms the results of several prior
behavioral studies in humans (Quamme, et al., 2004; Vann, et al., 2009; Yonelinas, et al.,
2002). The results contradict claims that recollection and familiarity were equally impaired in
amnesic patients (Amaral, et al., 1990; Wais, 2008; Wixted & Squire, 2004). The results
thus provide strong support that recollection and familiarity are neuropsychologically
dissociable processes. In line with the established literature for mild hypoxia (Cummings, et
al., 1984; Di Paola, et al., 2008; Duzel, Vargha-Khadem, et al., 2001; Hopkins, et al., 1995a,
1995b; Mecklinger, et al., 1998; Press, et al., 1989; Rempel-Clower, et al., 1996; Squire, et
al., 1990; Squire, et al., 1989; Yonelinas, et al., 2002; Zola-Morgan, et al., 1986) and ERP
effects (Curran, 2000; Friedman & Johnson, 2000; Rugg & Curran, 2007), the current results
add to a growing body of research supporting models that suggest recollection and familiarity
are supported by different medial temporal lobe structures (Diana, et al., 2007; Eichenbaum,
et al., 2007), i.e. especially the hippocampus (Duzel, Vargha-Khadem, et al., 2001; Fortin, et
al., 2004) and perirhinal cortex(Bowles, et al., 2007; Sauvage, et al., 2008), respectively.
**Tables & Figures**

**Figure 1.0** Subjects made recognition memory judgments to a mixture of studied words and words that were new to the experiment. For each test item, subjects first made an item memory confidence judgment (i.e., is the item old or new to the experiment?), followed by a source memory confidence judgment (i.e., was the item encoded during the ‘animacy’ or ‘manmade’ conditions in the earlier study phase?). ERPs were recorded during the presentation of the test word, and classified according to the item and source memory responses.
## Table 1. Distributions of Item Recognition Responses for Controls and Patients

<table>
<thead>
<tr>
<th>Controls (N=6)</th>
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<th>Low</th>
<th>Guess</th>
<th>Low</th>
<th>High</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>confident new</td>
<td>confident new</td>
<td>confident old</td>
<td>confident old</td>
<td></td>
</tr>
<tr>
<td>Old Items (n=1200)</td>
<td>.04 (.04)</td>
<td>.08 (.03)</td>
<td>.09 (.06)</td>
<td>.29 (.12)</td>
<td>.50 (.14)</td>
</tr>
<tr>
<td>New Item (N=600)</td>
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<td>.35 (.13)</td>
<td>.21 (.16)</td>
<td>.20 (.08)</td>
<td>.06 (.03)</td>
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<table>
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<th>Patients (N=3)</th>
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<th>Low</th>
<th>Guess</th>
<th>Low</th>
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<tr>
<td></td>
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<td>confident new</td>
<td>confident old</td>
<td>confident old</td>
<td></td>
</tr>
<tr>
<td>Old Items (n=600)</td>
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<td>.20 (.16)</td>
<td>.14 (.03)</td>
<td>.29 (.06)</td>
<td>.35 (.16)</td>
</tr>
<tr>
<td>New Items (n=300)</td>
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<td>.40 (.32)</td>
<td>.17 (.10)</td>
<td>.21 (.14)</td>
<td>.12 (.16)</td>
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</table>

## Table 2. Distributions of Source Recognition Responses for Controls and Patients

<table>
<thead>
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<th>Source Memory</th>
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<th>Unknown</th>
<th>Correct</th>
<th>Confident correct</th>
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<tr>
<td>Controls (n=1200)</td>
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<td>.14 (.06)</td>
<td>.32 (.12)</td>
<td>.24 (.12)</td>
<td>.25 (.12)</td>
</tr>
<tr>
<td>Patients (n=600)</td>
<td>.02 (.03)</td>
<td>.19 (.08)</td>
<td>.54 (.14)</td>
<td>.22 (.02)</td>
<td>.03 (.02)</td>
</tr>
</tbody>
</table>
Figure 2. Behavioral Performance on Tests of Item Recognition and Source Memory. Recognition accuracy (left panel) is plotted on the y-axis as the proportion of hits minus false alarms. Source memory accuracy (right panel) is plotted on the y-axis as the percentage of source memory hits minus source memory false alarms. Patients (N=3) were impaired relative to Controls (N=6) on both item and source memory, but retained the ability to perform item recognition above chance, while remaining unable to perform accurate source memory discriminations beyond chance.
Figure 3. Neurophysiology of Patients (N=3) and Controls (N=6) for Item Recognition Confidence. (Top panel) Difference wave topographies of item memory confidence responses of “5” vs. item memory confidence responses of “4” to old items for patients (top row) and controls (bottom row). Both patients and controls showed an FN400 that was maximal at the fronto-central electrode site Fc1, and which occurred from 400-600ms; whereas a prominent left parietal effect was evident in the control group from 600-800ms, but not in the patients. The LPC magnitude extended to most scalp regions, but exhibited an electrical maxima at left parietal sites (Bottom left panel) ERP difference waves of patients and controls for item 5 - item 4 memory contrast at left parietal electrode site P3, 600-800ms latency of LPC highlighted with dashed blue box. (Bottom right panel) Mean amplitudes of the difference wave of item 5 – item 4 confidence responses at mid-frontal electrode Fc1 during the 400-600ms latency, and left parietal electrode P3 during the 600-800ms latency.
Figure 4. ERPs of Item Recognition Confidence for Patients (N=3) and Controls (N=6). (Top panel) FN400 effects at mid-frontal electrode (Fc1). FN400 latency of 400-600ms is shown in dashed blue box. (Bottom panel) Parietal effects at left parietal electrode (P3), LPC latency of 600-800ms is shown in dashed blue box. The y-axis indicates microvolts (mV), and the x-axis is the recoding epoch (-200 to 1500 ms).
Figure 5. Neurophysiology of Patients and Controls for Source Memory Responses. (Top panel) Topographic maps of difference waves for Source Correct – Source Incorrect responses. Epochs during which recollection-related effects were evident are indicated by the red dashed box; epochs where significant negative going effects were evident are indicated by the blue dashed box. (Bottom Panel) ERPs of Source Correct and Source Incorrect responses at left parietal electrode site (P3).
Figure 6. ERPs for right parietal and left frontal effects of negative-going potentials related to source memory responses. (Top Panel) ERPs for patients (N=3) reveal a negative-going ERP effect for correct source memory responses at 800-1000ms and 1000-1200ms epochs (indicated by blue dashed boxes). (Bottom panel) ERPs for Controls (N=6) show no significant differences in source memory responses during 800-1000ms and 1000-1200ms latencies, but alternatively reveal more positive-going potentials for correct source responses during earlier latencies of 400-600ms and 600-800ms.
Supplemental Materials

S1. ERPs Associated with Accurate Source Judgments for Low Confidence Recognition. Topographic maps of the same contrast used in (R. Addante, et al., Submitted) (i.e.: item4 with source correct vs. correct rejections) are shown in Controls. Negative going ERPs at right parietal sites from 800-1000ms and 1000-1200ms is consistent with the same pattern found in a group of 25 healthy undergraduate subjects (R. Addante, et al., Submitted) and proposed to be a correlate of “contextual familiarity”. There is no evidence of an LPC from 600-800ms in either group, despite accurate source memory responses.
Chapter 5: Discussion & Concluding Remarks

Summary of Results

In summary, accurate source memory responses are preceded by an increase in theta oscillations at mid-frontal regions [i.e. Chapter 2], and it is selectively disrupted in amnesic patients with likely damage to the hippocampus [i.e. Chapter 4]. The pre-stimulus mid-frontal theta is predictive of a later left parietal theta activity during memory retrieval [i.e. Chapter 2], and recollection of item and source memory elicits an LPC effect at left parietal regions as well [i.e. Chapter 3]. However, when recollection is unavailable accurate source memory judgments can be still be made, possibly supported by a distinct cognitive process of context familiarity [i.e.: Chapter 3]. The neuropsychological dissociations of recollection and familiarity evident from ERP results of Chapter 4 provides strong evidence that long term episodic memory is comprised of separable dual processes, and that after mild amnesic damage, accurate recognition memory can be successfully achieved in the absence of recollection.

In Chapter 2, mid-frontal pre-stimulus theta was shown to precede successful recollection (as measured by both item and source memory), but not item familiarity (Addante, et al., 2011). This pre-stimulus effect at mid-frontal sites predicted accurate recollection on ensuing retrieval trials, and recollection on the ensuing trials was supported by elevated theta power at left parietal regions during the memory retrieval. A potential account of these effects is that mid-frontal pre-stimulus theta supports the left parietal network related to memory retrieval. This dynamic interaction between brain regions across time windows appears to reflect the delicate interaction of ongoing spontaneous neural activity and how we respond to environmental stimuli in order to achieve successful source
memory. Therefore, successful source memory retrieval requires sufficient levels of baseline theta power, which may be a prerequisite condition for optimal memory performance.

**In Chapter 3**, high and low confidence source memory judgments were found to be supported by two electrophysiologically distinct processes. Whereas correct high confidence source memory was associated with a late positive component indicative of recollection, correct low confidence source memory was associated with a late onset negative going ERP that was distinct from both recollection and familiarity based responses. The results indicate that correct source memory responses can be observed even in the absence of recollection. Thus, while recollection of source memory relies upon pre-stimulus theta to drive post stimulus theta effects [i.e. Chapter 2, (Addante, et al., 2011)], ERPs revealed that recollection is not a required process of source memory, and source memory can be achieved by alternative processing supported by distinct neurophysiology. Additionally, results of this chapter provide a critical proof of concept that this paradigm is effective at eliciting both the FN400 and LPC effects in item recognition confidence ratings, and that these effects are functionally dissociable. This is consistent with the large body of literature for ERP effects of episodic memory, and extends their validity and the generalizability of those findings. Moreover, it provides an essential platform from which to interpret the results of Chapter 4, by establishing that both the FN400 and LPC appear to be present and associated with differential familiarity- and recollection-based processing in this paradigm.

**In Chapter 4**, experiments recording ERPs of neuropsychological patients during item and source memory tasks revealed that source memory depends critically upon the medial temporal lobe structures affected in amnesia, but that item recognition memory remains relatively preserved, as indexed by behavioral measures. Despite the deficit in
source memory, subsequent analysis of patient ERPs suggested that some accurate source judgments in amnesic patients may be supported by contextual familiarity due to a similar pattern of negative going ERPs as was characterized in Chapter 2. Most importantly, evidence from this experiment revealed that mild hypoxia patients showed no evidence of recollection related neurophysiology (i.e.: severe disruption of LPC) that was alternatively observed in both healthy age-matched controls and which was previously established in the healthy twenty-five young adults studied in Chapter 3, but yet the amnesic patients still showed normal brain activity for familiarity-related processing (i.e.: FN400). This is interpreted as consistent with dual process models of memory.

To conclude, the preceding four chapters addressed the following three broad questions outlined in the Introduction concerning the fundamental nature of human memory:

1. **How does it work? – What conditions are needed for engaging memory networks?**
   - Pre-stimulus theta activity prior to retrieval cues enhances memory success

2. **What is it made of? – What processes enable experiencing ‘Mental Time Travel’?**
   - Separable components of recollection and familiarity contribute to successful memory retrieval, at different times and exhibiting different scalp topographies.

3. **How is it organized in the brain & what goes wrong in certain types of amnesia?**
   - Recollection and familiarity are dissociable dual processes of memory.
   - Hypoxic amnesia is due to impairments in recollection, but not familiarity.

**Future Directions:**

**Pre-stimulus Effects on Cognitive & Behavioral Performance**

What are the subcortical regions that are supporting pre-stimulus theta effects for source memory? fMRI evidence of memory encoding has found that BOLD activity in the
hippocampus was associated with accurate subsequent memory, and similar results from MEG has been found to be localized to medial temporal lobes. However, to date the results of Chapter 2 remain the only available data of pre-stimulus activity prior to memory retrieval (not encoding stages), and this data was at the level of the human scalp. It is likely that the pattern of activity reported in Chapter 2 relies in part upon supporting activity in subcortical regions, most likely the medial temporal lobes, but this question remains largely unexplored.

Key advances will require careful fMRI experiments designed to assess the sensitive timescale of pre-stimulus effects, augmented by high-resolution analyses of medial temporal lobe sub-regions.

Also critical to this question will be experiments that test neuropsychological patients with damage to different medial temporal, as well as frontal and parietal structures of the brain, to investigate any differences in pre-stimulus EEG activity that may be related to memory deficits. An extension of that work could be searching for effects of pre-stimulus states in psychiatric diseases such as schizophrenia, depression, and ADHD, since it may be possible that their cognitive deficits may be related to a broader disruption of endogenous networks of neural activity. Finally, intracranial EEG recording from human pre-surgical patients could also provide essential converging information about the role that temporal lobe structures (as well as other cortical areas measured with grid or depth electrodes) may exert in successful cognitive performance.

A related application of this work will be investigations that explore how pre-stimulus effects may affect other forms of cognitive and behavior performance on complex tasks ranging skill learning, motor memory, and the role of cognitive control in reducing and enhancing these effects. Additionally, it will be important to assess how theta levels may be
trained in various manners, from neurofeedback and cognitive control to more invasive methods like transcranial direct current stimulation (tDCS) in order to both enhance accurate memory and reduce memory errors in normal populations, as well as to improve memory deficits in amnesia populations with various neuropsychiatric disorders.

Implications of influencing memory by changing levels of theta extend also to modulating negative memories by decreasing levels of theta, which could prove essential in approaching detrimental memory conditions such as post-traumatic stress disorder, which would benefit from a deceased likelihood of spontaneous memory retrieval. More speculatively, it is possible that positive societal applications can be made by elevating pre-stimulus theta levels in order to enhance eye witness testimony retrieving critical item and source memory information from episodic memory in legal proceedings. On a more subtle level, it will be important for future work to characterize the distinctions and interactions of pre-stimulus states with related observations of default modes, retrieval modes, and other ongoing brain states that are thought to play influential roles in cognition and behavior.

Relation of Memory Encoding to Memory Retrieval

What is the role that encoding plays in episodic memory, and how does EEG activity during this stage affect and relate to memory retrieval performance and EEG activity during retrieval? ERP correlates of memory encoding have been identified as Dm effects for basic episodic recognition, but it is not yet known whether the encoding ERPs can be distinguished for stimuli which is later recollected or familiar, as have been identified during retrieval (Rugg & Curran, 2007). While the dissociable ERP correlates of recollection and familiarity during retrieval have been well established and have been influential in guiding current
theory, emerging research now suggests that the basis for these cognitive dissociations at retrieval could be due to how the brain processes incoming stimuli when they are initially encoded into memory (Fernandez et al. 1999; Rugg et. al. 1998; Ranganath et. al. 2004; Staresina and DaVachi 2006). That is, fMRI experiments have reported a double dissociation of recollection and familiarity-predictive activity during encoding, such that hippocampal activity during encoding predicts later source recollection, whereas perirhinal activity during encoding predicts subsequent increases in recognition confidence (Ranganath et. al. 2004; Kensinger and Schacter, 2006; see DaVachi 2006 for review; see Gold et. al., 2006 and Squire et. al. 2007 for alternative results and explanations).

Regarding whether the encoding processes related to recollection and familiarity are distinct, if separable ERP correlates of recollection and familiarity during encoding can be identified as robustly as they have been for retrieval is currently unknown. Yet, ERP methodology is ideally suited for assessing this concern because they provide both a direct physiological measure of the complex neural processes involved in recognition encoding and retrieval, and they provide information with very high temporal resolution – a characteristic that is particularly important in separating cognitive processes expected to exhibit rapid temporal dynamics - which is difficult for other techniques, such as fMRI to capture. However, surprisingly little is known about how ERP activity during encoding is related to these forms of recognition. As Friedman, Nessler, and Johnson, Jr. (2007) pointed out, “a clear gap in the literature is in understanding how encoding processes influence subsequent retrieval, and ERPs recorded during both stages of memory should prove especially useful in addressing this critical issue.”
In one of the earliest ERP studies of memory encoding Paller et. al. (1987) found that the ERPs for words that were subsequently recognized was more positive going that those that were subsequently forgotten, an effect he referred to as the Difference in Subsequent Memory, or DM effect (for a review see Rugg 1995). Only a few subsequent experiments have examined whether the DM effect might differ for recollection and familiarity based responses, and the results from these studies have been somewhat mixed (Yovel & Paller, 2004; for reviews see Rugg, 1995; Friedman et al., 2000.; Friedman et. al. 2007). For example, using a remember/know paradigm, a number of studies have found similar DM effects of both ‘remember’ and ‘know’ responses (Senkfor and Van Petten, 1998; Friedman and Trott, 2000; M.E. Smith,1993). Although the DM effects are generally larger for remember than know responses, these graded results are consistent with single process accounts of memory encoding.

However, results from some other studies have suggested that there may be subtle differences in the DM effects for recollection and familiarity. For example, Mangels et. al. (2001) found that an earlier DM effect (i.e., with a left frontocentral distribution) was related to both remember and know responses, but that a later effect (i.e., with sustained posterior and frontal distributions) was larger for remember responses. This later effect was attributed to the elaborative processing necessary for conscious recollection. This is consistent with a recent study that found a similar later DM effect that predicted correct source memory performance (Cansino et al., 2008). In addition, Duarte et. al. (2004) found that subsequent familiarity-based recognition was associated with a left-lateralized enhanced positivity and observed at anterior scalp sites from 300 to 450 ms, whereas subsequent recollection was associated with a topographically distinct right-lateralized positivity at anterior scalp sites.
from 300 to 450 ms and bilateral activity from 450 to 600 ms. Although there are many procedural differences across these studies that may have contributed to the variable outcomes, the variability may be related in part to differences in how subjects used the remember and know responses in these different experiments, and thus it will be important in future studies to examine the encoding effects using more objective and specific measures of recollection and familiarity.

**Characterizing the Functional Significance of Context Familiarity**

Currently, the general concept of context remains elusive for the field to arrive at a consensus operational definition, as it is inherently different between experimental conditions and sensory modalities. Future work will be needed to further characterize the role of negative going ERPs that appear to be associated with accurate memory of contextual information, and how this supports source memory decisions. Importantly, research is needed to dissociate item familiarity from contextual familiarity within an experimental manipulation, a task which again faces inherent challenges. Additionally, critical work remains to be done to provide a clear link between the medial temporal lobe structures, such as the parahippocampal cortex, to context familiarity processing. One possible implication of this is that contextual familiarity may not depend upon the hippocampus, but could be supported by the parahippocampal gyrus that remains intact in mild hypoxia, and in this way, accurate source memory may be available from support of this medial temporal lobe region when hippocampal-dependent recollection is not available. A key approach to accomplishing this task will be fMRI studies which utilize similar paradigms as those used in Chapters 1 and
2 for eliciting conditions of context familiarity that is independent from recollection processing of source memory.

Providing further evidence that context familiarity is independent from both recollection and item familiarity processes will be a significant advance as well, as will being able to map these processes onto potentially differential supporting brain regions. Another interesting approach would be to explore for the oscillatory correlates of contextual familiarity processing. Though challenging, addressing these issues remains possible and is an exciting area of potential for future research.

**Addressing Amnesia in Neuropsychological Patients**

Of course, a primary goal of future research must be to not just further characterize the functional role of memory in healthy young adults, but to be able to apply this knowledge to helping those with both mild and severe forms of memory problems. Memory loss is a key facet of many neurological and psychiatric diseases ranging from epilepsy, schizophrenia, depression, diabetes, post-traumatic stress disorder, cardiovascular disease, Alzheimer’s, disease as well as other forms of dementia, brain damage, chronic stress, and normal aging. Thus, memory loss has debilitating effects on the lives of millions of people, as well as devastating effects on familial relationships and quality of life. Indeed, memory is a fundamental fabric of the human experience, and when we lose it we lose a certain aspect of our self. Our past experiences shape both our current condition and our future directions, and without this critical reference and ability of “mental time travel” we are disadvantaged for living the most enriching and fulfilling lives possible.
By studying memory in amnesic patient populations, as a field we can further develop treatments and strategies which will have a significant impact on improving patients’ lives. A critical step in basic research will be a thorough examination of the encoding related ERPs in patient groups such as hypoxia, for example, which can indicate whether their amnesia can be traced back to encoding problems or whether they are best characterized as retrieval deficits: essential information to drive translational therapeutic strategies for clinical patient applications. Additionally, research studying intracranial and scalp EEG can provide unique insights into the fundamentals of memory function and dysfunction in the brain. Future applications studying the benefits of cognitive training, ERP biomarkers of early memory problems (e.g.: reduced FN400 & LPC effects), and theta power enhancement all offer promising new directions of translational research in clinical patient populations. Most importantly to any future progress on improving memory problems in amnesic populations, though, is the continued willing participation of patients in research studies, as well as the control subjects who provide the critical comparisons. The value of their participation simply cannot be overstated; and their generosity, patience, and good will to assist in our research endeavors into the complex processes of the human mind is a vital factor in any successes that we may find. Their contributions are very much appreciated.


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