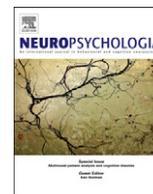




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Neurophysiological evidence for a recollection impairment in amnesia patients that leaves familiarity intact

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ABSTRACT

In several previous behavioral studies, we have identified a group of amnesic patients that, behaviorally, appear to exhibit severe deficits in recollection with relative preservation of familiarity-based recognition. However, these studies have relied exclusively on behavioral measures, rather than direct measures of physiology. Event-related potentials (ERPs) have been used to identify putative neural correlates of familiarity- and recollection-based recognition memory, but little work has been done to determine the extent to which these ERP correlates are spared in patients with relatively specific memory disorders. ERP studies of recognition in healthy subjects have indicated that recollection and familiarity are related to a parietal old-new effect characterized as a late positive component (LPC) and an earlier mid-frontal old-new effect referred to as an 'FN400', respectively. Here, we sought to determine the extent to which the putative ERP correlates of recollection and familiarity are intact or impaired in these patients. We recorded ERPs in three amnesic patients and six age matched controls while they made item recognition and source recognition judgments. The current patients were able to discriminate between old and new items fairly well, but showed nearly chance-level performance at source recognition. Moreover, whereas control subjects exhibited ERP correlates of memory that have been linked to recollection and familiarity, the patients only exhibited the mid-frontal FN400 ERP effect related to familiarity-based recognition. The results show that recollection can be severely impaired in amnesia even when familiarity-related processing is relatively spared, and they also provide further evidence that ERPs can be used to distinguish between neural correlates of familiarity and recollection.

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1. 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 is always associated with a generalized episodic memory impairment, or whether some forms of episodic memory may be spared. There is evidence that at least some amnesic patients may 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,

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2010; Diana, Yonelinas, & Ranganath, 2008; Eichenbaum, Yonelinas, & Ranganath, 2007; Holdstock et al., 2002; Holdstock et al., 2008; Mayes et al., 2004; 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, some amnesic patients with MTL damage suffer from significant deficits in both recollection and familiarity, leading some to speculate that the MTL operates as a memory system that is equally involved in all forms of episodic memory (Gold et al., 2006; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Song, Wixted, Hopkins, & Squire, 2011; Squire, Zola-Morgan, & Chen, 1988; Squire & Zola, 1997; Wais, 2008; Wais, Wixted, Hopkins, & Squire, 2006; Wixted & Squire, 2011).

Behavioral evidence indicates that patients who became amnesic following mild hypoxia may exhibit selective impairments in recollection with a sparing of familiarity (Aly et al., 2010; Diana et al., 2008; Quamme et al., 2007, 2004; Simons et al., 2004; Vann et al., 2009). Several anatomical and histological studies have indicated that mild cases of hypoxia can lead to

hippocampal damage that often leaves the surrounding medial temporal lobe structures intact (Cummings, Tomiyasu, Read, & Benson, 1984; Di Paola et al., 2008; Duzel, Vargha-Khadem, Heinze, & Mishkin, 2001; Hopkins, Kesner, & Goldstein, 1995a; Hopkins, Kesner, & Goldstein, 1995b; Mecklinger, von Cramon, & Matthes-von Cramon, 1998; Press, Amaral, & Squire, 1989; Rempel-Clower, Zola, Squire, & Amaral, 1996; Squire, Amaral, & Press, 1990; Squire, Amaral, Zola-Morgan, Kritchevsky, & Press, 1989; Zola-Morgan, Squire, & Amaral, 1986). Accordingly, evidence of selective recollection deficits in mild hypoxia patients can permit inferences about the relative roles of the human hippocampus and surrounding medial temporal lobe structures in recollection and familiarity. However, there are two critical limitations to the neuropsychological studies that have been conducted with these types of patients. First, only behavioral measures of recollection and familiarity have been obtained. Claims about recollection and familiarity in these patients would be considerably strengthened by converging evidence 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, Vargha-Khadem, & Mishkin, 2001), thus it is critical to determine whether the recollection deficits observed in these patients can be verified using measures such as tests of memory for source that do not rely so heavily on subjective reports.

Event-related potentials (ERPs) may provide a useful neurophysiological correlate of memory processes in amnesia. While ERPs do not reflect a direct 1:1 mapping of these underlying memory processes (because other cognitive processes may produce similar modulations of the measures (Paller, Lucas, & Voss, 2012), or the measures themselves may be insufficiently sensitive to detect the occurrence of the process in every case (Wang, de Chastelaine, Minton, & Rugg, 2011), in general ERPs are regarded as effective in providing the putative neural correlates of these cognitive processes. Several ERP studies of recognition have reported consistent double dissociations between ERP effects of recollection and familiarity that are spatially and temporally dissociable at the scalp (e.g.: Rugg, Mark, Walla, Schoerscheidt, Birch, & Allan (1998), for reviews see Curran (2000); Friedman and Johnson (2000), Rugg and Curran (2007), Mecklinger (2006) but also see Paller et al., 2012; Paller, Voss, & Boehm, 2007). Behavioral conditions that modulate familiarity are often associated with modulations of an ERP effect referred to as the ‘mid-frontal old-new effect’. This effect is manifest as a voltage difference between conditions evident at a negative ERP peak occurring approximately 400–600 ms following the onset of a retrieval cue, which is typically most pronounced at mid-frontal scalp sites (as such is often notated as an ‘FN400’ effect) (Rugg & Curran, 2007)¹. Recollection, in contrast, is associated with an ERP

effect referred to as the ‘parietal old-new effect’ (commonly observed as a Late Positive Component, noted as ‘LPC’). The LPC is measured as a positive ERP difference between conditions, observed between approximately 600–900 ms that is maximal over left parietal sites, such that recollected items are associated with a more positive ERP modulation than non-recollected items. Numerous studies have demonstrated that the FN400 and LPC occur at separate times, have different topographic distributions on the scalp, and are differentially sensitive to conditions that modulate familiarity and recollection, respectively Rugg & Curran (2007).

A few studies have used ERPs to characterize recognition memory in patients with extensive medial temporal lobe damage (Lehmann, Morand, James, & Schnider, 2007; Mecklinger et al., 1998; Olichney et al., 2000; Rugg, Roberts, Potter, Pickles, & Nagy, 1991; Smith & Halgren, 1989; Smith, Stapleton, & Halgren, 1986), but only one prior study (Duzel et al., 2001) has recorded memory-related ERPs in a patient expected to have selective recollection impairments. Duzel et al. studied a patient who had suffered a hypoxic event early in life that resulted in selective hippocampal atrophy with relative preservation of the surrounding medial temporal lobe cortex (Gadian et al., 2000; Vargha-Khadem et al., 1997). This patient showed no evidence of an LPC but did exhibit a normal FN400 in an old/new recognition task. Unfortunately, behavioral measures of recollection and familiarity were not obtained in that ERP study so it is difficult to link the ERP findings to separate recognition processes. Moreover, because the hypoxic event occurred at a very young age it is not known whether the same pattern of ERP effects would be obtained in patients who suffered MTL damage later in life (Manns & Squire, 1999; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Vargha-Khadem et al., 1997). That is, it is possible that his spared memory reflects, at least partially, developmental functional reorganization.

In the present study, we used ERPs to assess the extent to which the putative neural correlates of recollection and familiarity would be evident in mild hypoxia patients whom had previously demonstrated behavioral deficits in recollection. Because the debate concerning behavioral impairments of these patients (Montaldi & Mayes, 2011; Wixted & Squire, 2004, 2011; Wixted & Squire, 2011; Yonelinas et al., 2004) centers around whether or not they are impaired on the processes of recollection (Duzel et al., 2001; Gold et al., 2006; Manns et al., 2003; Quamme et al., 2004; Vann et al., 2009; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998; Yonelinas et al., 2002) and/or familiarity (Song et al., 2011; Stark & Squire, 2003; Wixted & Squire, 2004), the LPC and FN400 correlates are particularly well suited to assessing this with physiological measures. We predicted that if the patients suffer from a selective deficit in recollection, then they should 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 either reduced or unobservable². Additionally, to behaviorally characterize recognition in these patients, we used an item confidence and source recognition paradigm to test episodic memory, rather than relying on subjective report methods. This procedure was chosen

¹ An alternative view of the FN400 effect is that it may also be related to conceptual implicit memory, particularly for non-verbal materials such as faces, gabor patches, or complex geometric shapes (Paller et al., 2012; 2007; Voss, Lucas, & Paller, 2010; Voss & Paller, 2007). However, arguing against this account are multiple studies from different laboratories showing that the mid-frontal effect associated with familiarity can be dissociated from other priming-related ERP effects (Bridger, Bader, Kriukova, Unger & Mecklinger, 2012; Wiegand, Bader, & Mecklinger, 2010; Yu & Rugg, 2010; Woodruff, Hayama, & Rugg, 2006; Rugg et al., 1998; Curran & Hancock, 2007; Groh-Bordin, Zimmer, & Ecker, 2006; Groh-Bordin, Zimmer, & Mecklinger, 2005; Rosburg, Mecklinger, & Frings, 2011; Stenberg, Hellman, Johansson, & Rosen, 2009; Stenberg, Johansson, Hellman, & Rosen, 2010, see also commentary of Mecklinger, Frings, & Rosburg, 2012).

² Paller et al. (2012) noted that there is stronger evidence for a link between the FN400 and familiarity for verbal materials than there is for more complex materials such as gabor patches, faces, or complex geometric figures. Thus, we would expect to see an FN400 modulation associated with familiarity in the present study, which used verbal materials. Further, we employed an item recognition confidence paradigm similar to that used by both Yu & Rugg (2010) and Woodruff et al. (2006) whom each showed that the mid-frontal familiarity effect was dissociable from other ERP effects related to implicit memory (for similar demonstrations using other paradigms, see Rugg et al., 1998, Bridger et al., 2012, as detailed in Mecklinger et al., 2012). Thus, for the purposes of this study, if an FN400 effect was observed in this particular patient group it could be reasonably inferred that this reflected the putative electrophysiological correlate of familiarity-based processing (Rugg & Curran, 2007; Bridger et al., 2012).

because source memory has rarely been assessed in studies of hypoxia, and source memory confidence has not been assessed with the current patients.

2. Methods

2.1. 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 (O1 and O2, each age 52) 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 O3 (age 30) acquired a relatively circumscribed amnesic syndrome after recovering from a traumatic brain injury due to a car accident. The latter patient received a clinical MR scan, which exhibited evidence of medial temporal lobe atrophy restricted to the hippocampus (see Fig. 1). Table 2 provides the estimated gray matter volumes corrected for overall grey matter volume, for the right and left hippocampus, parahippocampal cortex, perirhinal cortex and entorhinal cortex for patient O3, along with 5 control subjects who were age-matched for this particular patient. Patient O3's medial temporal lobe volume estimates for grey matter were all within the normal range (2 Standard Deviations) of those found for the control subjects with the exception of the left and right hippocampal regions (which were substantially reduced in volume), and the left entorhinal cortex, which was larger than that seen in the controls. In addition, fluid attenuation inversion recovery (FLAIR) images showed a small area of white matter hyperintensity deep in the left occipital lobe. Neuropsychological profiles of each patient are detailed in Table 1.

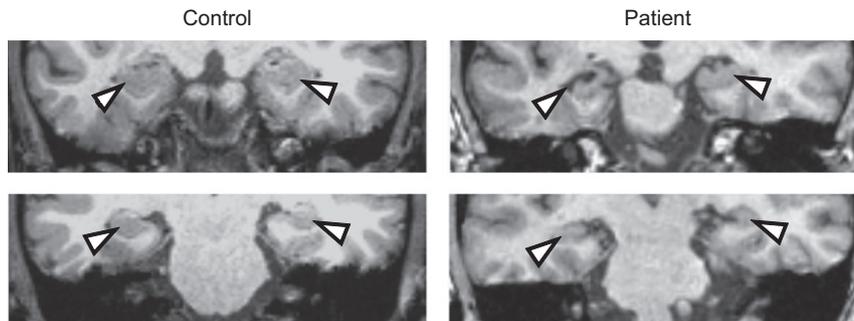


Fig. 1. Coronal MRI sections from patient O3 (right) and from one of the age matched controls (left). The hippocampus (arrows) was markedly reduced in volume in the patient, whereas other regions of the medial temporal lobe regions such as the perirhinal cortex, entorhinal cortex, and parahippocampal cortex showed no sign of atrophy (see Table 2 for quantification).

Table 1 Neuropsychological profiles of patients. Wechsler adult intelligence scale (WAIS) and the Wechsler memory scale—revised (WMS-R) yield mean scores of 100 in the normal population with a standard deviation of 15.

Patient	Age (years, at time of test)	Education (years)	WAIS-R IQ	WMS-R Attention	WMS-R Verbal	WMS-R Visual	WMS-R General	WMS-R Delay
O1	49	16	96	97	62	130	79	83
O2	50	13	94	96	94	77	87	80
O3	24	16	111	103	80	105	87	68

Table 2 Gray matter measures (i.e., gray matter volume/total gray matter volume) of medial temporal lobe regions in patient O3 and age matched controls. The hippocampus was significantly reduced in volume bilaterally in the patient. The parahippocampal, perirhinal and entorhinal cortices were in the normal range with the exception of the left entorhinal cortex which was larger in the patient than in the controls.

	Hippocampus		Parahippocampal cortex		Perirhinal cortex		Entorhinal cortex	
	Left	Right	Left	Right	Left	Right	Left	Right
Controls (N=5) (SD)	0.0053 (0.0002)	0.0050 (0.0002)	0.0041 (0.0003)	0.0038 (0.0003)	0.0037 (0.0006)	0.0040 (0.0005)	0.0016 (0.0002)	0.0020 (0.0003)
Patient O3	0.0041	0.0035	0.0034	0.0042	0.0051	0.0036	0.0037	0.0024

2.2. Procedures

The stimuli were words selected from the Medical Research Council Psycholinguistics Database (<http://www.psych.rl.ac.uk/MRCPsychDb.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 (Fig. 2). Subjects were seated approximately 44 in. away from the screen.

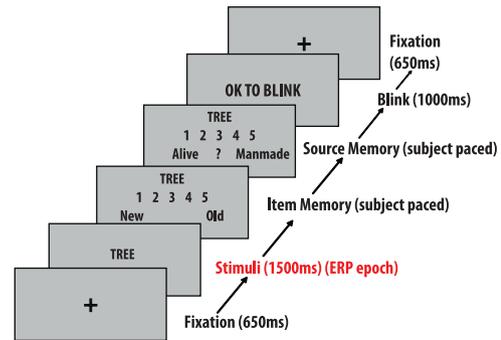


Fig. 2. Experimental design. Subjects made recognition memory judgments to a mixture of studied words and words that were new to the experiment. For each test item, subjects first made an item memory confidence judgment (i.e., is the item old or new to the experiment?), followed by a source memory confidence judgment (i.e., was the item encoded during the 'animacy' or 'manmade' task conditions in the earlier study phase?). ERPs were averaged relative to the onset of the test word, and binned according to the item and source memory responses.

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., Addante, Watrous, Yonelinas, Ekstrom, & Ranganath (2011), Addante, Ranganath, and Yonelinas (2012), 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 encoding 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 encoding blocks were presented, there was a delay of 90 min during which the electrode cap was applied before the retrieval phase of the experiment commenced.

ERPs were recorded while subjects made item and source recognition memory judgments. During retrieval, the 200 stimuli presented during the encoding phase randomly intermixed with 100 new words (lures) (Fig. 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 presentation of each probe word (stimulus duration = 1500 ms), subjects then made an item recognition judgment followed by a source 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 could only guess if old/new, 2 indicating it was probably new, and 1 indicating they were sure it was new (Fig. 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 a guess (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.

2.3. 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 1024 Hz. 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 ms before each probe word to 1500 ms following the onset of the probe. Baseline voltage was the mean voltage 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, 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. Two fronto-polar electrodes (Fp1, Fp2) located directly above the eyes and which were unrelated to the hypotheses of the current study (i.e., mid-frontal and left parietal sites) were found to have minor ocular aberrations in the patients, likely due to muscle

tension of their efforts to control blinks, and were removed from the data of both groups. An average of 88% of 'old' status ERP trials in patients were retained after artifact rejection (95%, 91%, & 77% for each of the 3 patients, respectively), while on average 94% of old item 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://erplab.org/erplab>), a plug-in toolbox of Matlab functions for EEGLAB software (Delorme & Makeig, 2004). ERPs were grand averaged to a baseline of the 200 ms 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.

Analyses of FN400 and LPC amplitudes focused on latency windows defined *a priori*, (c.f. Luck, 2005), based on the established ERP literature of familiarity and recollection-related effects (Curran, 2000; Friedman & Johnson, 2000; Rugg & Curran, 2007) and previous ERP results using the same paradigm (Addante et al., 2012). Therefore, we focused our analysis on the time periods of 400–600 and 600–900 ms to measure the FN400 and LPC effects, respectively, and to assess our primary hypothesis that the amnesic patients would show abnormalities of the LPC but not of the FN400. The established literature of ERP effects associated with recollection and familiarity-based processing also provided us with *a priori* defined regions of interest at which to assess effects during the aforementioned latencies, guiding our analysis to fronto-central electrode sites during the 400–600 ms latency for familiarity-related ERPs, and to left parietal sites during the 600–900 ms latency for recollection-related ERP activity. 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., Gruber and Otten (2010), Kim, Vallesi, Picton, and Tulving (2009), Otten, Quayle, Akram, Ditlew, and Rugg (2006), Addante et al. (2012)). Statistical tests are reported as two-tailed unless otherwise indicated: one-tailed tests were used during initial behavioral contrasts which were designed to assess if the mean of patients item memory performance was significantly greater than zero (Fig. 2), as well as when mean ERPs of correct source memories in controls were assessed to determine if they were significantly more positive going than ERPs of incorrect source judgments, since these instances were only expected to differ in one direction.

3. Results

3.1. Behavior

Item recognition. The item recognition confidence ratings for old and new items are presented in Table 3. Recognition

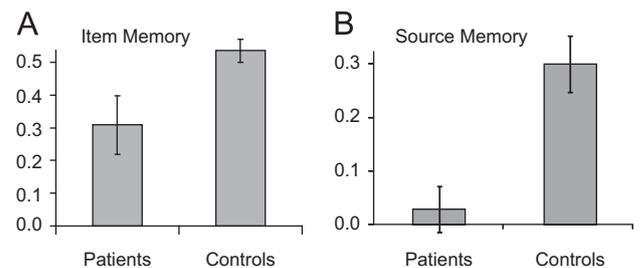


Fig. 3. Behavioral Performance on Tests of Item Recognition and Source Memory. (A) Recognition accuracy is plotted on the y-axis as the proportion of hits minus false alarms. (B) Source memory accuracy is plotted on the y-axis as the percentage of source memory hits minus source memory false alarms, where the point of 0.0 represents chance-level performance. Error bars depict the standard error of the mean.

Table 3
Distributions of item recognition responses for controls and patients.

	High confidence new	Low confidence new	Guess	Low confidence old	High confidence old
Controls (N=6)					
Old items	.04 (.04)	.08 (.03)	.09 (.06)	.29 (.12)	.50 (.14)
New item	.18 (.12)	.35 (.13)	.21 (.16)	.20 (.08)	.06 (.03)
Patients (N=3)					
Old items	.02 (.01)	.20 (.16)	.14 (.03)	.29 (.06)	.35 (.16)
New items	.10 (.06)	.40 (.32)	.17 (.10)	.21 (.14)	.12 (.16)

performance (Fig. 3) 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). As expected, the patients were significantly impaired at item recognition when compared to controls ($t(7)=2.96$, $p=.022$). Nonetheless, the patients performed item recognition at significantly above chance levels, $t(2)=3.49$, $p=.036$ (one tailed), which demonstrates some preservation of item recognition ability. Note that the same pattern of results was observed when d' values were assessed.

Closer inspection of the high and low confidence recognition responses (Table 3) 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 produced fewer responses to old items than did the controls (.50 vs. .35) (Table 3), and more high confidence false alarms to new items (.12 vs. .06). Recognition accuracy (i.e., hits minus false alarms) for the high confidence recognition responses 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. Note however, that these differences might also be explained as a simple decrease in overall memory performance. To assess this possibility further, the average confidence data in Table 2 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), rather than fitting the average ROCs for each group, the differences between patient and control estimates were not significant ($p's > .05$), likely due to the small group sizes. The fact that these effects were not statistically significant indicates that the behavioral evidence from item recognition confidence responses that patients suffered from a specific 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 4, as well as the proportion of high and low confidence item hits contributing to each level of source confidence judgment. Source recognition performance (Fig. 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, source memory accuracy was impaired in the patients relative 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 ($t(2)=.822$, $p=.497$). Furthermore, for the

high confidence hits (correct item 5 judgments), source accuracy was significantly above chance for the controls ($M=.78$, $t(5)=7.64$, $p=.0003$, one-tailed) but was not significantly above chance in the patients ($M=.61$, $t(2)=1.19$, $p=1.78$, one-tailed), whereas for the low confidence hits (item 4), source accuracy for controls was only marginally significant as better than chance level performance ($M=.61$, $t(5)=1.74$, $p=.07$, one-tailed) and for patients this was not significantly different from chance ($M=.45$, $t(2)=-1.20$, $p=.176$, one-tailed). To the extent that source recognition relies heavily on recollection, the results indicate that the patients exhibited a pronounced recollection deficit.

3.2. Electrophysiology

Item recognition memory. Item recognition ERPs were examined by contrasting the old item trials with low confidence versus high confidence recognition responses to old items (i.e., low confidence hits vs. high confidence hits; 4 vs. 5 responses). These response bins were selected because they were expected to reveal effects related to both recollection and familiarity, which may inform the pattern of behavioral responses observed. That is, on average, both recollection and familiarity would be expected to be higher for items recognized with high confidence responses than for items recognized with low confidence. There was a sufficient number of high- and low-confidence hits responses for each patient and control (after artifact rejection there were a mean number of 50 trials for low confident '4' responses and 62 trials for high confident '5' responses for patients, and the minimum number for any patient was 41 trials). ERP effects were measured as voltage differences between conditions at *a priori* determined latencies (400–600 ms and 600–900 ms) and electrode locations (mid-frontal and left parietal sites). The time windows were selected based on prior studies of recollection and familiarity (Addante et al., 2012; Curran, 2000; Friedman & Johnson, 2000; Rugg & Curran, 2007; Rugg et al., 1998). The specific electrodes analyzed were selected based upon results of prior work, and were observed to also be where the average memory effects (of the entire sample) were maximal in the current study, which confirmed the consistency of the observed results with the known characteristics of these effects from the literature.

ERPs for high and low confidence hits are shown in Fig. 4 for the patient and control groups at mid-frontal electrode site Fc1 and left parietal site P3. Fig. 5 displays the qualitative scalp distribution of the difference waves for these item recognition effects (i.e., high- minus low-confidence hits). Both patients and controls showed an FN400 that was maximal at the fronto-central electrode site Fc1, and which occurred from 400 to 600 ms; whereas a prominent left parietal effect was evident in the control group from 600 to 900 ms, but not in the patients. The LPC magnitude extended to most scalp regions, but exhibited voltage maxima at left parietal sites (Fig. 5A). More specifically, the figures illustrate that for the control subjects, ERPs for confidently recognized item hits were more positive than ERPs for low confidence item hits (i.e., warmer colors). Differences between the two trial types emerged approximately 400 ms post-stimulus

Table 4
Distributions of source recognition responses for controls and patients.

Source memory	High confidence, but incorrect	Low confidence, incorrect	Unknown	Low confidence, correct	High confidence, correct
Controls	.05 (.05)	.14 (.06)	.32 (.12)	.24 (.12)	.25 (.12)
From item 4	.01 (.00)	.08 (.06)	.06 (.04)	.13 (.09)	.01 (.01)
From item 5	.05 (.05)	.05 (.03)	.05 (.07)	.10 (.05)	.24 (.14)
Patients	.02 (.03)	.19 (.08)	.54 (.14)	.22 (.02)	.03 (.02)
From item 4	.00 (.00)	.09 (.04)	.11 (.04)	.08 (.04)	.00 (.00)
From item 5	.02 (.03)	.10 (.05)	.08 (.05)	.14 (.03)	.02 (.02)

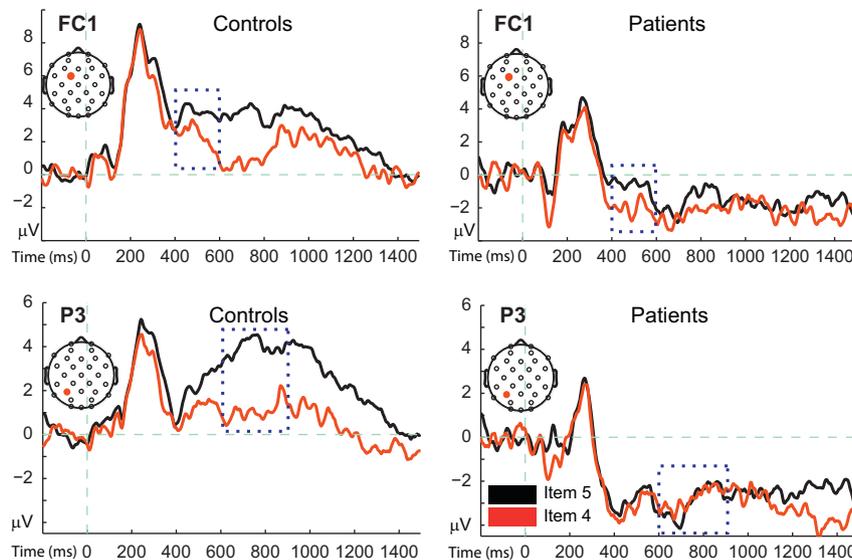


Fig. 4. ERPs of Item Recognition Confidence for Patients ($N=3$) and Controls ($N=6$). (Top panel) FN400 effects at mid-frontal electrode (Fc1). The time window used to analyze the FN400 (400–600 ms) is highlighted in dashed blue box. (Bottom panel) Parietal effects at left parietal electrode (P3), LPC latency of 600–900 ms is shown in dashed blue box. ERP amplitudes (in microvolts) are plotted on the y-axis, and time relative to onset of the test item is plotted on the x-axis (–200 to 1500 ms). High confidence hits (“5” items) are plotted in black and lower confidence hits (“4” items) are plotted in red.

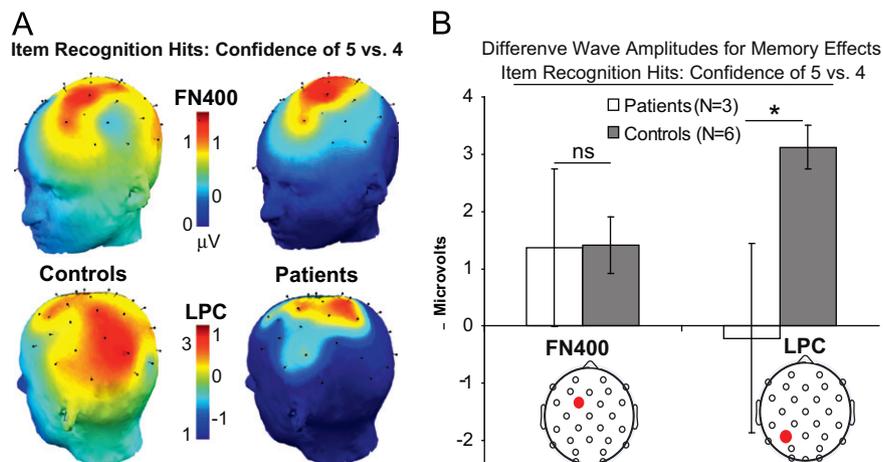


Fig. 5. Topographic Distribution and Quantification of FN400 and LPC effects. (A) Scalp topographies are plotted for the average amplitude of ERP differences between high vs. low confidence hits during the 400–600 ms (FN400) and 600–900 ms (LPC) time windows for patients and controls. Note that FN400 effects are similar in magnitude and scalp topography for both patients and controls, whereas LPC effects are attenuated for patients. (B) Mean amplitudes of ERP differences between high- and low-confidence item hits for patients (open bars) and controls (filled bars). At left, FN400 amplitudes are plotted for mid-frontal electrode Fc1 during the 400–600 ms latency, and at right the LPC effect is plotted for left parietal electrode P3 during the 600–900 ms latency. Error bars depict the standard error of the mean, ‘*’ indicates statistically significant differences, ‘ns’ indicates non-significant values.

onset, with a broad fronto-central distribution which then gradually grew larger in magnitude and shifted to exhibit a left posterior distribution by 600–900 ms; whereas the patients also exhibited a broad fronto-central distribution from 400 to 600 ms which alternatively diminished in magnitude by the later time of 600–900 ms (Fig. 5A). This pattern of results is consistent with a large body of literature that has revealed an early mid-frontal FN400 associated with familiarity and a later LPC related to recollection, (e.g., Rugg et al., 1998; for reviews see Curran, 2000; Friedman & Johnson, 2000; Rugg & Curran, 2007; Mecklinger, 2006), and suggests a severe disruption of the LPC generators in our amnesic patient group.

To quantify the ERP effects related to recollection and familiarity, we focused on the mid-frontal FN400 by examining fronto-central electrode Fc1 during the 400–600 ms time window, and the LPC by examining left parietal electrode P3 during the 600–900 ms window (Fig. 5B). We conducted separate 2×2 ANOVAs

on ERP amplitudes during the FN400 and LPC effect latencies, using group (patients vs. controls) as a between subjects factor and recognition confidence (high vs. low) as a within-subjects factor. From 400 to 600 ms, there was a main effect of confidence $F(1, 7)=5.76$, $p=.047$, indicating that there was a significant FN400. Importantly, there was no evidence of a confidence by group interaction, ($F(1, 7) < 1$), indicating that FN400 amplitudes did not significantly differ across patients and controls (Fig. 5B). In contrast, for the LPC there was a main effect of confidence, $F(1, 7)=6.1565$, $p=.042$, but this was qualified by a significant confidence by group interaction, $F(1, 7)=7.273$, $p=.031$. Subsequent analyses indicated that this interaction arose because only the control subjects exhibited a significant LPC effect ($t(5)=-6.39$, $p=.001$), whereas there was no evidence of this effect in the patients ($t(2)=.087$, $p=.938$).

Our next analyses directly contrasted the FN400 and LPC effects in the patients and controls. We quantified mean ERP

amplitude differences between high-confidence (“5”) and low confidence (“4”) hits for the FN400 (Fc1 electrode, 400–600 ms) and the LPC (P3 electrode, 600–900 ms; shown in Fig. 5B), and subjected them to a group (patient vs. controls) by ERP effect (FN400 and LPC) ANOVA. This analysis revealed a significant

interaction [$F(1, 7)=13.253, p=.008$], consistent with the conclusion that the LPC was disproportionately disrupted in the patients. The relationship between patients and controls for FN400 and LPC effects is shown graphically in Fig. 5B.

Could the absence of an LPC in the patients be due to insufficient power, particularly given that there were only three patients? The significant interaction between group and ERP effect verifies that the patients exhibited a relatively selective disruption of the recollection compared to the familiarity ERP effect. But how confident can we be that the LPC was completely eliminated in the patients, and that the FN400 was completely normal? To address these questions we conducted a Bayes Factor analysis (Rouder, Speckman, Sun, Morey, & Iverson, 2009; Vilares & Kording, 2011; Zhang & Luck, 2011) which revealed that it was 2.66 times more likely that the LPC was absent in the patients than the alternative possibility that there was a positive LPC. In addition, it was 2.34 times more likely that the patients exhibited a normal FN400 effect, than the alternative possibility that the patients exhibited an impaired FN400. Thus, despite the limited number of patients in the current study, the observed dissociation between recollection and familiarity appears to be quite complete.

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). After artifact rejection there were a mean number of 43 and 132 trials in each of these two bins, and the minimum number for any subject was 37. For control subjects this contrast was expected to provide a measure of recollection, and so it should be related to a LPC similar to that observed in the item recognition analysis. In contrast, given that the patients were not significantly above chance at making source judgments, and they were expected to have recollection impairments, we did not expect to see an ERP correlate of recollection.

Fig. 6 shows the ERPs of the source memory effects in the controls and patients at left parietal electrode P3. In line with the LPC effects seen in the item recognition analyses, for the controls the source correct trials produced a more positive going ERP than the source incorrect trials at P3 during the 600–900 ms time window. In contrast, no LPC was evident for the patients, and

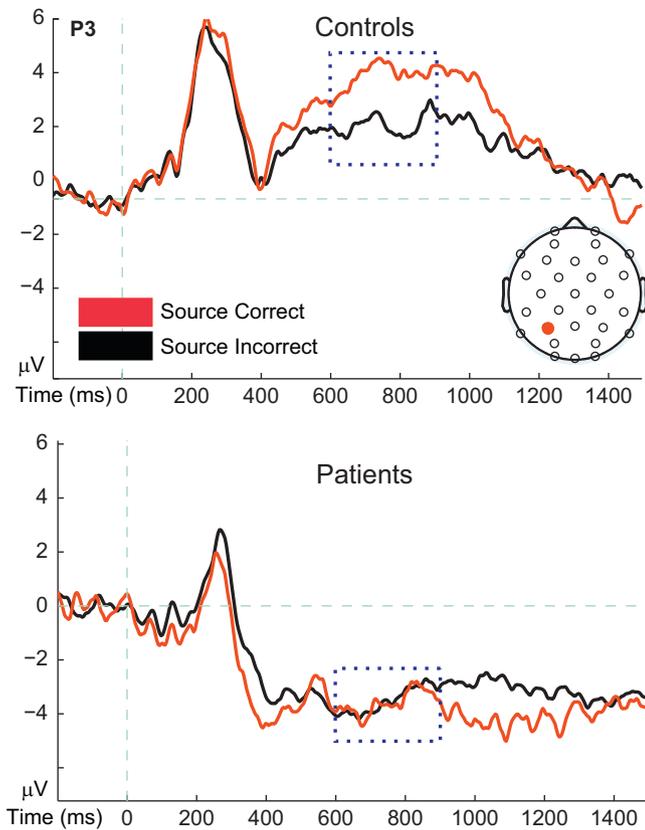


Fig. 6. ERP correlates of source memory accuracy for patients and controls. ERPs are plotted for the left parietal electrode site (P3). The LPC time window (600–900 ms) is indicated by the blue dashed box.

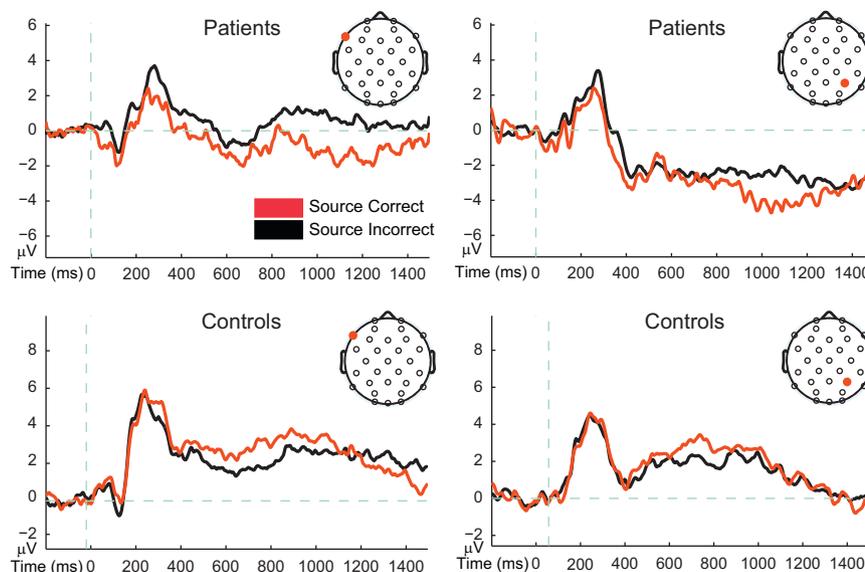


Fig. 7. Late negative ERP shift related to source memory accuracy in patients. (Top Panel) ERPs for patients ($N=3$) reveal a prolonged negative shift for ERPs associated with correct source memory responses. ERPs are shown for left frontal (F7) and right parietal (P4) sites. (Bottom panel) This effect was attenuated in ERPs for Controls ($N=6$) at the same sites.

instead ERPs associated with accurate source decisions were associated with a later negative-going potential over right posterior regions (i.e., 800–1000 ms and 1000–1200 ms epoch of Fig. 6 and Fig. 7), which we followed up by assessing activity during these 200 ms epochs based upon prior work (Addante et al., 2012). Planned *t*-tests were performed on the P3 electrode, and indicated that there was a significant source memory LPC in controls, $t(5)=2.18$, $p=.04$ (one tailed), but not in patients ($t(2)=-.108$, $p=.46$, one tailed), which is consistent with the same pattern observed in the item recognition ERPs. A 2x2 ANOVA also revealed that source correct ERPs were also more positive going than source incorrect ERPs during the 400–600 ms latency at fronto-central sites for both patients and controls ($F(1, 7)=5.76$, $p=.047$) as would be expected, and this did not interact among group ($F(1, 7)=.002$, $p=.965$).

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 800–1000 ms and 1000–1200 ms period for accurate source memory judgments, which was not seen in the controls (Figs. 6 and 7). This effect was not expected, so to further characterize this late negativity in the patients, we conducted an exploratory 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. 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 (Fig. 7). There were no significant differences in Controls for source memory from 1000 to 1200 ms at either left frontal, $t(5)=.66$, $p=.53$, or right parietal electrode sites, $t(5)=.32$, $p=.72$.

4. 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. The results indicated that the LPC effect, which has been consistently linked with recollection, was absent in the hypoxia patients, whereas the FN400 effect, which has been linked with familiarity, did not reliably differ from that of controls. That is, in the controls, we identified the FN400 and the LPC components that have been associated with familiarity and recollection, respectively (Addante et al., 2012; Curran, 2000; Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Friedman & Johnson, 2000; Rugg & Curran, 2007; Mecklinger, 2006; Yu & Rugg, 2010; Woodruff et al., 2006; Leynes, Landau, Walker, & Addante, 2005; Rugg et al., 1998; Wilding & Rugg, 1996; Vilberg, Moosavi, & Rugg, 2006; Curran, DeBuse, Woroch, & Hirshman, 2006). The FN400 was observed for controls in the item recognition contrast, whereas the LPC was observed in both the item recognition and the source memory contrasts for this group. Importantly, in the patient group, the ERP correlate of familiarity (FN400) was normal, whereas there was no evidence of the ERP correlate of recollection (LPC).

The present results provide converging evidence with behavioral studies suggesting that mild hypoxia can be associated with severe deficits in recollection even when familiarity may be relatively spared (Aly et al., 2010; Holdstock, Mayes, Isaac, Gong, & Roberts, 2002; Holdstock, Mayes, Isaac, Gong, & Roberts, 2002;

Holdstock et al., 2008; Mayes et al., 2004; Quamme et al., 2004; Vargha-Khadem et al., 1997; Yonelinas et al., 2002). The results also parallel results showing that hippocampal lesions in rats eliminate the contribution of recollection but spare familiarity-based recognition (Fortin, Wright, & Eichenbaum, 2004; Sauvage, Fortin, Owens, Yonelinas, & Eichenbaum, 2008).

The ERP results concur with those of Duzel et al. (2001), who demonstrated that a hypoxic patient ("Jon") with selective hippocampal damage showed a selective reduction in the LPC, along with a normal FN400 effect (Duzel et al., 2001). However, Jon's hippocampal damage occurred shortly after birth, so it could be argued that his spared familiarity was due to neural reorganization over the course of development (Manns & Squire, 1999; Vargha-Khadem et al., 1997). Unlike Jon, the patients in the current study suffered hypoxic or traumatic brain injury damage much later in life, indicating that selective recollection impairments are not limited to cases in which amnesia occurs early in development. The results of the present study also resemble the findings of a prior ERP study of chronic amnesia patients (Olichney et al., 2000). Using an incidental learning paradigm in which both semantically congruous and incongruous words are repeated, they found significantly reduced LPC effects (old-new congruous word voltage differences), but normal N400 repetition effects were elicited by the semantically incongruous words.

As noted in numerous studies, the FN400 and LPC effects have differences in time course, scalp topography, and functional correlates, consistent with the idea that the effects are generated by different neural sources (Friedman & Johnson, 2000; Rugg & Curran, 2007). Our results revealed that the LPC was selectively and disproportionately attenuated in the amnesia patients, who also showed no behavioral evidence of recollection. These results support dual process models of recognition memory (Yonelinas, 1994, 1999; Yonelinas, Aly, Wang, & Koen, 2010; Yonelinas, Dobbins, Szymanski, Dhaliwal, & King, 1996; Yonelinas & Parks, 2007) which assume that recollection and familiarity reflect distinct, neurally-dissociable memory processes. The results are problematic for single process accounts that would suggest that amnesia is always associated with equivalent impairments in familiarity and recollection (Donaldson, 1996; Dunn, 2004; Wixted & Mickes, 2010).

This study, like most studies of amnesic patients, is limited by small sample size. Importantly however, the current findings rested on significant interactions between the patients and controls, and thus provided strong statistical support for there being selective reductions in the recollection component in light of a normal familiarity component. In addition, a Bayes Factor analysis suggested the lack of an LPC in the patients was unlikely to simply reflect insufficient statistical power. A related limitation is that based on the current study alone we cannot draw strong conclusions about the location of the neural generators of the FN400 and LPC effects that we observed. That is, scalp ERPs do not allow us to determine with any precision the neural generators of the observed ERPs (i.e., the Inverse Problem) (Luck, 2005; Niedermeyer & Lopes da Silva, 1982). In addition, without histological data it is difficult to say with certainty which brain regions were involved for the amnesic patients. Volumetric data indicated that patient 03 had medial temporal lobe damage that was restricted primarily to the hippocampus (Table 2, Fig. 1), which is consistent with models that assume that the hippocampus is critical for recollection but not familiarity (e.g., Aggleton & Brown, 1999; Eichenbaum, Otto, & Cohen, 1992), however, it was not possible to obtain MRI measures of brain structure in the other patients (patient 01 and 02), due to their defibrillators. Nevertheless, interpretation of the available evidence for patient 03, together with an established literature of hypoxic effects, suggests that the observed memory deficits were linked at least in part to damage to the hippocampus. Many previous studies have

found that although severe hypoxia can be associated with medial temporal lobe damage outside the hippocampus, volumetric and histological studies have indicated that in mild cases of hypoxia (such as the patients studied in this experiment) the damage is restricted primarily to the hippocampus (Cummings et al., 1984; Di Paola et al., 2008; Hopkins et al., 1995a, 1995b; Reed & Squire, 1997; Rempel-Clower et al., 1996; Vargha-Khadem et al., 1997; Zola-Morgan et al., 1986). These results are also highly consistent with prior work across various species and methodologies indicating that the hippocampus is critical for recollection but not familiarity (e.g., Duzel et al., 2001; Fortin et al., 2004; Sauvage et al., 2008; Vargha-Khadem et al., 1997; Yonelinas et al., 2002; Ranganath et al., 2004; Curran et al., 2006). Thus, the current results, taken together with the existing literature supports models which assume that recollection relies upon the integrity of the hippocampus while familiarity can be supported by the surrounding MTL cortex (Eichenbaum et al., 2007; Montaldi & Mayes, 2010).

Although the literature linking the LPC to recollection (Curran, 2000; Curran & Doyle, 2011; Friedman & Johnson, 2000; Rugg & Curran, 2007; Rugg et al., 1998), and linking familiarity to the FN400 is quite extensive (Curran, 2000; Friedman & Johnson, 2000; Mecklinger, 2006; Rugg & Curran, 2007), neither the LPC nor FN400 can be expected to provide a direct 1:1 mapping to recollection or familiarity, respectively. For example, one view mentioned earlier is that the FN400 may also index fluent processing of a concept, which could drive conceptual implicit memory (Paller et al., 2007, 2012; Paller et al.; Voss & Federmeier, 2011) (see Footnotes 1 & 2). Importantly however, if the FN400 is sensitive to conceptual fluency, this does not necessarily contradict research finding a strong relationship between the FN400 and familiarity (Bridger et al., 2012; Wiegand et al., 2010; Groh-Bordin, Zimmer, & Ecker, 2006; Mecklinger, Frings, & Rosburg, 2012; Stenberg, Hellman, Johansson, & Rosen, 2009; Stenberg, Johansson, Hellman, & Rosen, 2010; Mecklinger, 2006; Yu & Rugg, 2010; Woodruff et al., 2006; Rugg et al., 1998; Rugg & Curran, 2007). Behavioral research has demonstrated that conceptual fluency can drive both implicit measures of conceptual priming and explicit measures of familiarity (e.g., Wagner, Stebbins, Masciari, Fleischman, & Gabrieli, 1998; Yonelinas, 2002). Furthermore, the hypoxic patients studied here were shown to exhibit normal conceptual implicit memory, in contrast to other amnesic patients with damage documented to the perirhinal cortex, whom have shown conceptual implicit memory impairments (Wang, Lazzara, Ranganath, Knight, & Yonelinas, 2010). Although further work needs to be done to clarify the factors that contribute to familiarity and conceptual implicit memory, the available evidence is consistent with the idea that, at least for verbal materials, conceptual fluency (possibly indexed differentially by the N400, e.g. Wolk et al., 2004; Bridger et al., 2012) might contribute to both (Wang & Yonelinas, 2012).

One unexpected finding in the current study was that the patients exhibited a significant negative-going ERP effect from 800 to 1200 ms in the source correct vs. source incorrect contrast (Figs. 6 and 7), which was not observed in the control subjects. The functional significance of this effect for the patients is unclear, but it is worth noting that we observed a similar ERP modulation in a recent study of item and source recognition in healthy young subjects (Addante et al., 2012). In that study, high confidence item hits ('item 5' responses) that were associated with correct source judgments elicited an LPC, whereas low confidence item hits ('item 4' responses) that were associated with accurate source judgments instead elicited a later-onsetting ERP negativity similar to the what we observed in the patients.

One possible account for this finding is that correct source responses for low confidence item recognition may not be based on either recollection or item familiarity, per se, but rather they

may reflect neural processing associated with 'contextual familiarity' (e.g., Addante et al., 2012). That is, recent models of MTL function (Diana, Yonelinas, & Ranganath, 2007; Eichenbaum et al., 2007; Montaldi & Mayes, 2010) assume that recollection relies upon the hippocampus whereas item familiarity relies upon the perirhinal cortex. In addition, however, the parahippocampal cortex is assumed to support memory for contextual information (Diana, Yonelinas, & Ranganath, 2012). It is possible that the late negativity we observed in the current patients (Fig. 7) and in the low confidence source responses in healthy subjects (Addante et al., 2012) is related to the re-processing of the two encoding contexts that made up the two different source discrimination tasks at retrieval. That is, if a test item leads the related study context question to come to mind more fluently than the non-studied question (e.g., "I don't recollect any specific details about the study event, but I automatically thought about the fact that the item was manmade, so maybe I made a man-made judgment about the word during study"), this could support low confidence source memory responses. This account of the later negative ERP effect is admittedly speculative, so future studies that test these and competing ideas are needed to both advance and refine our understanding of contextual familiarity.

In sum, the current results provide electrophysiological evidence that amnesia can result in a deficit in recollection that leaves familiarity-based recognition preserved. The ERP findings of this neuropsychological dissociation join an extensive body of behavioral findings showing that recollection and familiarity are functionally and neurally distinct.

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