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A critical role of the human hippocampus in an electrophysiological measure of implicit memory

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Abstract

The hippocampus has traditionally been thought to be critical for conscious explicit memory but not necessary for unconscious implicit memory processing. In a recent study of a group of mild amnesia patients with evidence of MTL damage limited to the hippocampus, subjects were tested on a direct test of item recognition confidence while electroencephalogram (EEG) was acquired, and revealed intact measures of explicit memory from 400–600ms (mid-frontal old-new effect, FN400). The current investigation re-analyzed this data to study event-related potentials (ERPs) of implicit memory, using a recently developed procedure that eliminated declarative memory differences. Prior ERP findings from this technique were first replicated in two independent matched control groups, which exhibited reliable implicit memory effects in posterior scalp regions from 400–600 msec, which were topographically dissociated from the explicit memory effects of familiarity. However, patients were found to be dramatically impaired in implicit memory effects relative to control subjects, as quantified by a reliable condition $\times$ group interaction. Several control analysis were conducted to consider alternative factors that could account for the results, including outliers, sample size, age, or contamination by explicit memory, and each of these factors were systematically ruled out. Results suggest that the hippocampus plays a fundamental role in aspects of memory processing that is beyond conscious awareness. The current findings therefore indicate that both memory systems of implicit and explicit memory may rely upon the same neural structures – but function in different physiological ways.

1.1 Introduction

Since the seminal studies of famous amnesic Patient HM (Scoville and Milner, 1957) (for reviews and updated findings, see Annese et al., 2014; Corkin, 2002), traditional models of memory systems have held that the medial temporal lobe (MTL) is was critical for explicit, consciously declared memory, but was not necessary for implicit memory (Squire, 2009;

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Suthana and Fried, 2012) operationalized as a non-conscious form of memory in which a prior encounter with a given stimulus influences the subsequent identification, production or classification of the same stimulus (Schacter et al., 2007). As such, implicit memory is often identified through a variety of experimental paradigms as a change in behavior or neural activity upon repeated representation of stimuli that is evident without subjects' conscious awareness of its re-presentation. This MTL distinction between conscious and non-conscious memory systems has been borne out through decades of neuropsychological, neuroimaging, electrophysiological, and animal studies (Eichenbaum et al., 2007; Gabrieli, 1998; Squire et al., 2007). However, this framework has gradually begun to erode (Chun and Phelps, 1999; Hannula and Greene, 2012; Maguire and Mullally, 2013).

A wide range of studies have established the MTL, and hippocampus in particular, to be critically associated with explicit memory processing, since subjects with lesions here exhibit deficits on explicit memory tasks but leave implicit memory performance relatively unimpaired (for reviews, see Cohen and Eichenbaum, 1993; Eichenbaum et al., 2007; Squire and Zola, 1997; Suthana and Fried, 2012). Alternatively, implicit memory has largely been considered dependent upon neocortical regions such as the frontal cortex (Schacter et al., 1993; Schacter et al., 2004; Schacter et al., 2007; Tulving and Schacter, 1990), based upon evidence that patients with hippocampal damage retain intact implicit memory (Hamann and Squire, 1997; Levy et al., 2004; Schacter et al., 1993) and from neuroimaging studies implicating other neocortical regions in support of implicit memory processes (Gotts et al., 2012b; Wagner et al., 2000). Nevertheless, fMRI studies have also revealed that MTL activity can differentiate memory signals that are not consciously accessible to subject's explicit reports of recognition (Daselaar et al., 2006b; Hannula and Ranganath, 2009; Kirwan et al., 2009a; Manns and Squire, 2001), raising the possibility that the hippocampus may play a more critical role in implicit memory than the idiosyncratic role typically ascribed (e.g.: Corkin, 2002; for review see Hannula and Greene, 2012). In line with this, some models have proposed the hippocampus to be a common substrate for forms of both implicit and explicit memory processing (Berry et al., 2008a, b; Berry et al., 2012; Cermak, 1997; Moscovitch, 2008; Reber, 2013; Sheldon and Moscovitch, 2010; Taylor and Henson, 2012), but this has yet to be experimentally confirmed in human lesion studies.

Studies of implicit memory in neuropsychological patients have been essential to current models of memory (Chun and Phelps, 1999; Corkin, 2002; Gabrieli et al., 1999; Hamann and Squire, 1997; Rosenbaum et al., 2014; Schacter and Church, 1995; Schacter and Graf, 1986), but have also been limited by a heavy reliance upon behavioral methods, and more broadly by challenges to isolating implicit memory effects independent from explicit memory activity (for discussion, see Voss et al., 2012). Integration of eye-tracking methods has provided critical new insight into the role of the hippocampus, revealing involvement in unconscious memory processing for associative and relational binding (Hannula and Ranganath, 2009), and researchers have noted the need for electrophysiological methods to better inform current models (i.e.: Hannula and Greene, 2012; Hannula et al., 2005). Electroencephalogram (EEG) is a critical method for understanding memory systems due to its high temporal resolution to capture direct neural activity corresponding to cognitive processes, (e.g.: Addante et al., 2012a; for review, see Rugg and Curran, 2007), and the possibility has been raised that other measures such as electrophysiology could be more

sensitive than the traditional behavioral methods for detecting implicit memory differences in neuropsychological patients (i.e.: Blaxton, 1992; Jernigan et al., 2001; Ostergaard, 1999); for review see Berry et al., 2008b).

One of the impediments in neuropsychological research is that, to date, there has been a paucity of studies collecting electrophysiological data of implicit memory in amnesia, and this stands in stark contrast to the wide extent to which electrophysiology has been particularly influential in advancing understanding of explicit memory (Duzel et al., 2001; Ekstrom et al., 2003; Fernandez et al., 1999; Hafting et al., 2005; Heit et al., 1988, 1990; Smith and Halgren, 1989; Smith et al., 1986; Suthana et al., 2012). However, a recent event-related potential (ERP) measure of implicit memory was recently developed that identifies implicit memory differences in neural activity by holding explicit memory responses equivalent between studied and unstudied trials- and which was dissociable from explicit memory processing (Woodruff et al., 2006; Yu and Rugg, 2010; see Methods section 2.8). While this neural measure of memory is well-suited for eliminating the confounds that can contaminate implicit memory with other explicit memory processes that have plagued prior approaches (for review see Voss et al., 2012), it has yet to be applied to amnesia patients.

The present research re-examined an existing EEG dataset of amnesic patients and control subjects (Addante et al., 2012a), and applied a recently-developed technique for isolating neural activity for memory without awareness (Woodruff et al., 2006; Yu and Rugg, 2010). The patients had been previously found to have intact familiarity forms of explicit memory despite recollection-related deficits linked to hippocampal damage (Addante et al., 2012a). Through this ERP analysis, and a series of systematic control analyses, convergent evidence is provided that reveals an electrophysiological deficit of implicit memory processing in a group of mild amnesia patients that leaves familiarity based explicit memory intact.

2.1 Methods

2.2 Subjects

The subjects studied in the current experiment have been reported previously (Addante et al., 2012a; Addante et al., 2012b), from which the data was re-analyzed using a new analysis technique applied in the present study. ERP data was thus re-examined from three groups of subjects: a group of 3 amnesia patients; a group of 6 age-matched control subjects whom were also matched to the patients on factors of gender, education, and verbal IQ (Table 1) (Addante et al., 2012a); and an additional group of 25 healthy younger adults whom had completed the same task in a prior study (Addante et al., 2012b). 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, and were reported previously as having medial temporal lobe damage limited to the hippocampus (Addante et al., 2012a; Supplemental Figure 1). Neuropsychological profiles of each patient are detailed in Table 1. Age-matched controls were recruited from among hospital employees and volunteers, surrounding retirement communities, and patients' spouses, and had no history of neurological or psychiatric disease.

2.2.1 Younger adult control group—The young adult group consisted of twenty-five healthy right-handed undergraduate students (eight males) recruited from the University of California–Davis Psychology Department subject pool, and received credit for participation. As described in (Addante et al., 2012b), subjects were free from neurological, visual, motor, or other medical disorders. Mean age of the young adult group was 20.12 years ($SD = 2.18$) and their mean education level was 14.13 years ($SD = 1.5$). This was comparable to patient and control groups, whose mean education levels were also 15 years ($SD = 1.73$) and 15.17 years ($SD = 2.14$), respectively; whereas the mean ages of the patients and control group were matched at 44.7 ($SD = 12.70$) and 45.8 ($SD = 13.6$) years, respectively. Hence, for purposes of the current study this younger group of adults served effectively as a parallel control group matched on education and gender proportion, albeit differing in age. An analysis between control groups of established ERP effects as a function of age was conducted, and revealed that ERP effects did not vary as a function of age (see Results section 3.2, footnote ⁴), and both groups of controls also performed equivalently in item recognition as well (pHit - pFalseAlarm; young controls: $N = 25$, $M = .60$ ($SD = .14$); age-matched controls: $N = 6$: $M = .54$ ($SD = .09$), $t(29) = 1.11$, $p = .276$. Thus, since there were no differences among control groups in either behavior or physiology as a function of age, and they were therefore treated as equivalent groups of different sample sizes.

2.3 Stimuli

The stimuli were words 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)) 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 S1). Subjects were seated approximately 44 inches away from the screen.

2.4 Procedures

The experimental procedure for the paradigm has been reported previously (Addante et al., 2012a; Addante et al., 2012b). 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 (Addante et al., 2011; 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

⁴A 2×2 ANOVA with factors of conditions (old, new) and group (mid-age, young adult) revealed a significant main effect of Condition ($F(1,29) = 4.75$, $p = .038$) but no effect of Group ($F(1,29) = 1.54$, $p = .590$) or any Condition × Group interaction ($F < 1$), indicating that groups did not differ in implicit memory effects as a function of age (see also section 3.5 for similar results for ERP effects of explicit memory).

appeared in the test phase. After the 4 encoding blocks were presented, there was a delay of approximately 90 minutes, during which the electrode cap was applied before the retrieval phase of the experiment commenced.

ERPs were recorded during an item recognition memory test. During retrieval, 200 stimuli presented during encoding were randomly intermixed with 100 new words (lures) presented in 6 test blocks of 50 stimuli each. 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 (Figure S1). Controls performed item recognition tests at above-chance levels (Table 2; see also (Addante et al., 2012a), and patients demonstrated intact familiarity relative to control subjects despite recollection impairments (Addante et al., 2012a). Subjects were also tested on source memory, but since patients performed at chance levels of performance, the present analysis collapsed across source responses to focus on item recognition, so as to be consistent with the prior findings by Yu & Rugg (2010).

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 alone on the screen in central fixation for 1500ms, during which time the subject viewed the stimuli. Subjects were also instructed not to blink nor respond while each stimulus was on the screen, so as to minimize any potential ocular and motor artifacts in the EEG. Accordingly, reaction time (RT) measures were not available for meaningful analysis, due to the instruction to withhold behavioral responses to the retrieval probe (1500ms) until the ensuing response prompt, in order to obtain the maximum available signal-to-noise ratio required for ERPs of small samples of patient populations (e.g., Luck, 2005, 2014). During retrieval, each of the item and source memory responses were 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, in order to make sure they understood instructions well and used the response scale correctly.

2.5 Electrophysiological Acquisition

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. 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 and vertical directions, and this data was used to eliminate trials contaminated by blink, eye-movement, or other related artifacts.

2.6 Electrophysiological Analyses

All EEG analyses were performed using functions from the EEGLab Toolbox for Matlab (Delorme and 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 stimuli, and was baseline subtracted from –200 to 0 msec. 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 and 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. As noted in Addante et al., (2012b), two fronto-polar electrodes (Fp1, Fp2) located directly above the eyes and which were unrelated to the hypotheses of the current study (i.e.: posterior 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.

2.7 Event-related potential (ERP) analyses

ERPs were averaged from the EEG data using ERPLAB software (Lopez-Calderon and Luck, 2014), a plug-in toolbox of Matlab functions for EEGLAB software. 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 ERP figures, consistent with prior ERP studies (Addante et al., 2012a; see Rugg & Curran, 2007 for review) that have assessed mean amplitude between two latencies (which effectively smoothes the point-by-point data from that window into a single value for that latency).

2.8 Implicit memory contrast

The purpose of the current study was to examine ERPs of implicit memory in an existing dataset of item recognition confidence responses given by amnesia patients. To do so, a technique for isolating implicit memory processing was utilized which had been used effectively in several earlier ERP studies of item recognition confidence (Woodruff et al., 2006; Yu and Rugg, 2010) to identify memory effects of repetition without subjective awareness. The technique contrasted ERPs as a function of the test item's status (old vs. new) while controlling for response category (recognition confidence) – and reported effects in posterior scalp regions. This approach was replicated identically in the current study as detailed below, and was then further extended by testing with a stringent validation procedure (see Results section 3.1).

The procedure for creating this modified old-new contrast for effects of repetition without awareness is as follows (see also Supplemental Figure 2). For each level of item recognition confidence (i.e.: 1 through 5), the trial type (i.e. old or new) that has the fewer number of trials is identified, and then that same number of trials is randomly selected from the other trial type (old, or new) for inclusion into the ERP analysis- thereby eliminating from

analysis all other trials of that response type. This procedure for selecting equivalent numbers of response trials is then repeated for each of the five levels of item recognition confidence, and overall modified 'Old' and 'new' conditions are then created by collapsing across each of the confidence bins for each status (old, new). Hence, the subjective experience of consciously reported memory indicated by each subject during the retrieval test is thereby equated for 'old' and 'new' conditions (Supplemental Figure 2).

This procedure included equivalent numbers of old trials from each encoding task. ERP differences among the modified conditions thus can be seen as reflecting memory-related neural activity for repetition without awareness. A stringent series of control analyses were performed to validate that this measure was not contaminated by inclusion of explicit memory responses (see Results section 3.1). For simplicity purposes, this modified old-new contrast for identifying effects of repetition without subjective awareness is hereafter referred to as 'implicit memory' effects. The mean numbers (and range) of trials forming the ERPs of each condition for patients and controls were 77 (65–89) and 58 (46–67), respectively, consistent with earlier studies. In prior work using this measure (Woodruff et al., 2006; Yu and Rugg, 2010), the analysis of interest was performed on activity during the time window of the FN400 effect, which for this study was from 400–600 msec for the subjects using this paradigm (Addante et al., 2012a)¹. Statistical tests are reported as two-tailed unless otherwise indicated.

3.0 Results

Mean amplitudes of old and new status items (see Methods) were assessed for a cluster of seven bilateral posterior sites (Pz, P3, P4, Po3, Po4, Cp1, Cp2). These sites were chosen in an unbiased manner to include bilateral posterior parietal sites consistent with similar sites included in prior reports for this ERP effect (Woodruff et al., 2006; Yu and Rugg, 2010). This posterior parietal region was consistent with a range of similar findings from several different laboratories reporting implicit memory effects at posterior parietal sites (Galli et al., 2010; Groh-Bordin et al., 2005; Lucas and Paller, 2013; Rugg et al., 1998; Swaab et al., 2002; Wolk et al., 2004). A 2×2 ANOVA with factors of memory condition (old, new) and group (patient, control) revealed a substantial condition by group interaction ($F(1,7) = 37.19$, $p < .001$) (Figure 1). Scatterplots representing amplitudes of the effect for every patient and control subject are also illustrated in Figure 1: the mean value for controls was 1.08 ($SD = .67$), and each patients' value was beyond 2 standard deviations from the mean of controls (and from the least of controls), indicating that the group effects cannot be attributed to an outlier patient that would be driving the observed condition × group interaction.

Follow-up t-tests revealed that similar to other findings of positive-going posterior ERP effects related to implicit memory (Groh-Bordin et al., 2005; Galli et al., 2010; Lucas and Paller, 2013; Rugg et al., 1998; Swaab et al., 2002; Wolk et al., 2004; Woodruff et al., 2006; Woollams et al., 2008; Yu and Rugg, 2010), in the control subjects here, the interaction was due to reliable old > new effects ($t(5) = 3.94$, $p = .007$). In contrast, patients exhibited reliable

¹The same results were also found when using the 300–500ms time window used by prior studies (Yu & Rugg, 2010; Woodruff et al., 2006).

negative-going posterior ERP effects (new > old; $t(2) = -6.5$, $p = .03$). Hence, the condition $\times$ group interaction was revealed to be a crossover interaction among groups, such that controls exhibited reliable effects in the positive direction, but patients exhibited statistically significant effects in the negative direction (Figure 1), indicating a substantial difference in the physiology for how implicit memory was functionally operating among patients and controls.

Visual inspection of the ERPs revealed a 400–800ms latency of the effect in controls and a 400–1400ms duration of the effect in patients. An exploratory, post-hoc analysis of these latencies confirmed that the effects were reliable during these latencies ($t(5) = 2.84$, $p = .036$; $t(2) = -8.17$, $p = .015$, respectively) and maintained the same spatial distribution as in the apriori-defined latency of 400–600ms (Supplemental Figure 3)². The ERPs of patients also exhibited typical characteristics of the common ERP component referred to as a ‘contingent negative variation’ (CNV) (Walter et al., 1964), in that it was evident as a sustained electrical potential following an early negative peak, maximal at the vertex, and was distributed over bilateral parietal regions (Mento, 2013; Tecce, 1972). The observation of the CNV here is consistent with prior findings identifying its role in recognition memory tasks (Leynes et al., 1998) as well as its well-characterized association with attention and expectancy (Tecce, 1972; Walter et al., 1964) – particularly so in this case since subjects were instructed to attend to test probe stimuli (i.e. an initial stimulus, or ‘S1’, see methods section 2.4 Procedure) and they were expecting to provide their motor response to the upcoming memory prompt (i.e. serving as the imperative stimulus, or ‘S2’) (see Supplemental Figure 1 for response paradigm; see Discussion section 4.4.2 for further review).

3.1.0 Controlling for explicit memory: validating the implicit memory measure

Despite the current contrast for identifying ERP effects related to implicit memory being successfully used in prior studies to dissociate activity from explicit memory (Woodruff et al., 2006; Yu and Rugg, 2010) (see Methods section 2.8, Supplemental Figure 2), it could be possible that effects from this contrast may be reflecting activity contributed from the few explicit memory responses that were included in the modified contrast. That is, it could, in principle, be possible that even the small number of high confidence explicit responses included in this measure may be contaminating the contrast with other forms of explicit memory processing such as familiarity (in patients) or recollection in the control subjects, which could theoretically produce the positive posterior scalp effects evident for this ERP contrast (Figure 1). For example, the posterior distribution of the effects in Figure 1 are similar to the posterior parietal distribution often reported for the LPC effects associated with recollection-related processing (Supplemental Figure 1; Addante et al., 2012a; 2012b; Rugg & Curran 2007). Since the prior studies using this paradigm did not address this issue (Woodruff et al., 2006; Yu and Rugg, 2010), several systematic follow-up analyses were performed next to determine the role, if any, that inclusion of explicit memory responses might have had on affecting the outcome of this procedure.

²Author thanks an anonymous reviewer for suggesting this analysis.

3.1.1 Matched strength of item confidence levels included in implicit memory contrast

For the first of these analyses, the same modified old-new contrasts were constructed for repetition without awareness as was done for the effects reported in Figure 1 (see Methods), but this time for high confidence '5' responses were excluded from both old and new modified conditions. Since prior studies with this paradigm have established that recollection is limited to the '5' responses (Addante et al., 2012a; Addante et al., 2012b), removing these trials completely eliminates the ability for recollection to be contributing to the resultant effects. When ERPs were assessed for this comparison of confidence levels collapsed from 1 through 4, there remained a significant main effect of memory condition in the controls ($t(5) = 4.45$, $p = .007$), but not in the patients ($t(2) = -1.84$, $p = .207$) (Figure 2, column 2). There also remained a significant condition $\times$ group interaction ($F(1,7) = 36.47$, $p = .0005$). Therefore, it is not possible for the implicit memory effects to be attributed to recollection (despite similar topographies). Next, both the '4' and the '5' response trials were excluded from each modified 'old' and 'new' condition (i.e.: high and low confidence explicit memory judgments were removed), thereby excluding any trials in which subjects reported explicit memory, and including only trials of which subjects indicated no explicit memory awareness [confidence responses of 1, 2, & 3, respectively]. This revealed the same pattern of ERP results, as a marginal old-new effect remained evident in posterior parietal sites of the control subjects ($t(5) = 2.67$, $p = .073$), but not in the patients ($t(2) = -1.14$, $p = .920$) (Figure 2, columns 3). Thus, the implicit memory effects cannot be attributable to explicit memory processing, such as residual recollection or familiarity.

3.1.2 Un-matched strength of item confidence levels included in implicit memory contrast

The final control analysis then used the same approaches of modified response exclusion as described above, but sought to do so when relative memory strength was even greater for 'new' items than it was for 'old' items³. Memory strength of new items was made to be even greater than that of old items by including the high confidence '5' responses for new items in the modified old-new contrast, but comparing those ERPs to ERPs of the modified 'old' condition that first excluded the high confidence '5' responses (Figure 2, column 4), and then also when the modified 'old' condition that excluded both the high and low confidence '5' and '4' responses, (Figure 2, column 5).

First, when the modified 'old' condition excluded only the high confidence 'old' responses (Old1–4) and was compared to the modified 'new' condition that included all five levels of memory responses (New 1–5), there still remained a significant positive old-new effect at posterior sites in control subjects ($t(5) = 4.11$; $p = .009$), a marginal effect within the patient group ($t(2) = -3.72$, $p = .065$), and a reliable condition $\times$ group interaction ($F(1,7) = 29.25$, $p = .001$) (Figure 2, column 4). Further, when the 'old' condition excluded both the high and low confidence hits (i.e. '4' and '5' responses, Old1–3) and was compared to the modified 'new' condition that included all five levels of memory responses (New 1–5), there was again a significant positive old-new effect at posterior sites in control subjects ($t(5) = 2.82$; $p = .037$), no reliable effects evident in the patient group ($t(2) = -1.87$, $p = .202$), and a reliable condition $\times$ group interaction ($F(1,7) = .11.57$, $p = .011$) (Figure 2, column 5).

³Author thanks Ben Bowles for this suggestion.

Hence, ERP differences of this implicit memory contrast are unaffected by inclusion or exclusion of high confidence memory responses. This finding validates the procedure described in the Methods section 2.8 for identifying implicit memory ERP effects related to repetition without awareness, and specifically extends it from existing usage in earlier studies (Woodruff et al., 2006; Yu and Rugg, 2010). Therefore, the positive-going ERP difference waves observed for controls and from which patients reliably differed (Figure 1) cannot be explained as reflecting differences attributable to explicit memory processing, familiarity, recollection, or recollection-related ERP effects (i.e.: late parietal component, LPC), and is indeed reflecting neural activity attributable to human memory without conscious awareness.

3.2 Controlling for sample size

It might be possible that the size of the impaired implicit memory effect observed in patients was a function of the small sample sizes in the patient and control groups. To address this issue, a permutation test was conducted on control data to examine how often one would expect to detect similar ERP effects between similarly-sized groups of $N=3$ and $N=6$. The data used in this permutation test was the old-new difference amplitudes from 400–600 ms at the cluster of 7 posterior electrodes for a larger sample of younger controls ($N=25$, $M = 21$) who had performed the identical experimental paradigm (Addante et al., 2012b) and were matched for the same levels of education (see methods section 2.2.1), which provided an independent sample of implicit memory effects that did not differ from that of the main control group⁴ (see also results section 3.5).

For each of 1000 iterations in the permutation test, data from 9 subjects were randomly selected (without replacement) from the group of 25 subjects, and 6 of these were randomly assigned as the pseudo-control group ($N=6$) while the remaining 3 were assigned as a pseudo-patient group ($N=3$). An independent-samples t -test was conducted comparing the old-new amplitude difference between the pseudo-control and pseudo-patient groups⁵. The 1000 t -values were used to create a null distribution of t -values, and the p -value for the control vs. patient contrast reported above was determined by examining how many values in this null t distribution fell below this observed value. The resulting null distribution had a mean between-group t -value of .442, and critical t -values of -2.20 and 2.75 , respectively, as estimated by the 95% confidence interval derived from the .025 and .975 quantiles (Figure 3). The observed t -value between groups of patients and controls was 6.10 ($p<.001$), as described earlier, and only 1 of the 1000 iterations fell above this t -value, indicating there was no difference between the two pseudo-groups in this analysis as a function of sample size. This finding from a non-parametric analysis provided strong evidence that the observed impairment of implicit memory (Figure 1) is attributable to neuropsychological factors of the patients and cannot be attributed to differences in sample sizes of the groups.

⁵Note that an independent-samples t -test assesses the computational equivalent of a condition $\times$ group interaction that is revealed in a 2×2 ANOVA (i.e.: reported above and in Figure 1). The between-group t -test approach for identifying condition $\times$ group interactions was used here because it provided a more parsimonious way to compute, communicate, and graphically represent the permutation results (Figure 3).

3.3 Topographic analysis of implicit and explicit memory

I next sought to verify that the results from the current study's assessment of implicit memory effects for repetition without awareness were consistent with the similar effects first reported by Yu & Rugg (2010) (i.e.: topographic dissociations between anterior and posterior regions of scalp for familiarity and implicit recognition related effects). In order to determine if the positive-going ERP effects of implicit recognition memory were occurring in spatially distinct, non-overlapping topographic distributions on the scalp from those for explicit familiarity-based memory (FN400, Addante et al., 2012b), and hence that each effect was thus reflecting different cognitive operations (Rugg and Coles, 1995; Wilding, 2006a), a topographic analysis of the memory effects was performed. Since such topographic analyses require larger sizes than the available age-matched control group, a larger group of healthy adults were assessed whom had performed the identical experimental paradigm ($N=25$) and were matched on education (see Methods section 2.2.1), behavioral performance, and physiology (Results section 3.2, footnote ⁴), but which were younger in age ($M = 21$) than the middle aged patients and controls ($M = 46$).

As was done by Yu & Rugg (2010), a $2 \times 2 \times 2$ ANOVA was conducted on range-normalized⁶ mean amplitudes with factors of Condition (a. explicit familiarity effect from 400–600ms reported in Addante et al, 2012b, [FN400: Old5 – Old4], b. implicit memory effect [modified old-new effect from 400–600ms, see Methods section 2.8, Supplemental Figure 2]), Electrode Region (a. anterior, b. posterior hemispheres), and a factor of Group (a. young controls $N=25$, b. age-matched controls $N=6$). Consistent with Yu & Rugg (2010), each hemisphere consisted of 11 electrode sites: [anterior: AF3, F7, F3, Fc5, Fc1, Fz, Af4, F4, F8, Fc2, Fc6], [posterior: Cp5, P7, Cp1, P3, Po3, Pz, Cp2, P4, Po4, Cp6, P8]). There was a significant condition $\times$ region interaction ($F(1,29) = 5.806$, $p=.02$) which did not interact with the factor of group ($F(1,29) = 1.336$, $p=.26$) (Figure 4). Inspection of Figure 4 confirmed this was due to the explicit effect exhibiting a mid-frontal topography, whereas the implicit recognition effect exhibited a posterior scalp distribution instead. This finding replicated the findings of Yu & Rugg (2010) that implicit memory effects were evident at posterior sites while explicit memory effects were evident at spatially distinct frontal sites. These results indicated that the ERP correlates of explicit familiarity and implicit recognition during the same latency (400–600ms) were occurring in significantly different scalp topographies for both groups (young and mid-aged adult), and hence can be inferred as reflecting dissociable cognitive operations (Rugg and Coles, 1995; Wilding, 2006b).

3.4.1 ERP Effects of Confidence

One consideration as an alternative possibility is that these neuropsychological patients may have simply been incapable of eliciting positive posterior scalp effects due to their brain damage or potential reorganization after injury. Indeed, a prior ERP study of explicit memory in these patients reported a complete impairment in the LPC effect associated with

⁶The procedure for a topographic analysis requires that the amplitude voltages of scalp effects be range-normalized (Rugg et al., 1998; Wilding, 2006). As noted by Yu & Rugg (2010), the practice of amplitude normalization prior to topographic analysis has been criticized (Urbach and Kutas, 2002). However, the criticisms of Urbach and Kutas – that normalization results in an error due to baseline artifact and the effects of residual noise – apply only when data are normalized with respect to root mean square amplitude and are not relevant to range-normalized data (Wilding et al., 2006).

recollective processing in posterior parietal scalp regions (Addante et al., 2012a). To assess for this possibility, I sought to provide experimental evidence to determine if the ability to exhibit intact positive ERP effects at posterior parietal scalp sites could be observed and demonstrably intact in this current group of patients. ERP effects of confidence (confident – unconfident responses, collapsed across memory status) have been previously shown to have a posterior parietal scalp distribution associated with the P300-family of ERP components (Curran, 2004; Woodruff et al., 2006), and hence provide a useful construct by which to test this alternative account of the data. Of key importance to the current study was that previous studies reported these ERP effects of confidence at posterior parietal regions similar to those regions identified for main effects in the present study. It was hypothesized that if patients retained cortical abilities to exhibit positive scalp effects in posterior parietal regions, then a positive ERP difference wave related to response confidence should be evident in both patients and controls, and similar to effects which have been previously linked to confidence in other ERP studies of item recognition (Curran, 2004; Woodruff et al., 2006)⁷.

ERP amplitudes were compared for high and low confidence responses that were collapsed across study status and thus invariant to memory accuracy, from 600–900ms (Otten and Donchin, 2000). A 2×2 ANOVA of the 7-site posterior cluster was performed with factors of condition (confident, unconfident) and group (patient, control). This revealed a significant main effect of condition ($F(1,7) = 11.472, p=.012$), indicating that ‘confident’ ERPs were more positive going than ‘unconfident’ ERPs, a marginal effect of group ($F(1,7) = 5.231, p = .054$) – indicating that ERP effects for control subjects were larger in general than ERPs for patients during this time period of 600–900ms (as was expected, see below and footnote⁷), but importantly, there was no condition × group interaction ($F(1,7) = .735, p=.42$) (Figure 5). Thus, results indicated that patients had intact positive-going ERP effects of confidence- at the same posterior parietal sites that they exhibited the negative-going effects of implicit memory (Figure 2). Thus, while patients exhibited smaller sized ERPs, they nevertheless *do* still retain intact basic neurophysiological abilities to generate positive posterior scalp ERP effects for the confidence-related differences between these ERPs. Therefore the consideration supposing a general inability to exhibit positive parietal activity (i.e., by virtue of cortical reorganization, etc.) cannot be a valid factor to account for the observed implicit memory deficit (Figure 3).

3.4.2 ERP Effects of Confidence: general ERP amplitudes

The finding noted above (section 3.4.1) of a marginal group difference in overall ERPs during late latencies of the epoch was a pattern of results that was expected based upon prior studies which have indicated reduced ERP amplitudes of P300 responses to stimuli in amnesia (Kishiyama et al., 2004; Knight, 1996; Knight and Scabini, 1998) (see footnote⁷). Nevertheless, it is possible that, more broadly, the marginal effect of group may suggest that the ERP effects of patients could be attributable to issues of lowered overall voltage

⁷The P300/P3 family of component has been known to be impaired in hippocampal patients as a function of novelty processing (Knight, 1996; Knight & Scabini, 1998), so amplitudes in general were expected to be attenuated for patients in this study as well, as was evident in Addante et al., 2012b. Critically, though, differences between confidence conditions (i.e. Curran, 2004; Woodruff et al., 2006) were still expected to be evident despite reduced voltages overall, since patients have impairments in memory, and not confidence per se.

capabilities, weaker strength of neural activations, and/or nonspecific reductions in cognitive processing of patients⁸. One line of evidence weighing against this possibility is that patients demonstrated comparable levels of overall activation magnitude for the memory-related differences (absolute magnitudes for patients: $M = 1.54$, $SD = .41$; controls: $M = 1.07$, $SD = .67$; $t(7) = -1.08$, $p = .317$). To further assess this issue amid confidence responses here, raw voltages for other well-established ERP effects of the N1 and P2 components that occur earlier in the epoch (Bengson et al., 2012; Johannes et al., 1995; Luck and Hillyard, 1994; Mangun and Hillyard, 1991) were also examined to determine if patients exhibited other evidence of nonspecific voltage differences (i.e. main effects of group) that would be consistent with the notion of weaker overall neural processing throughout the epoch, or whether this finding was evident only at the specific later latencies reported above for the P300.

ERPs for confident and unconfident conditions were assessed for both groups (patients, controls) with a 2×2 ANOVA for both the N1 and P2 early ERP components (150–200ms, 250ms, respectively), which revealed no evidence for group differences in overall ERP magnitude in either the N1 or P2 component (N1: effect of group: ($F(1,7) = 2.68$, $p = .146$; P2: effect of group: ($F(1,7) = 3.79$, $p = .092$). Hence, patients retain intact overall neural activation levels as controls, since both groups exhibited similar overall levels of neural processing for the confidence ratings. These findings provide convergent evidence that any differences in overall ERP magnitudes across groups are unlikely to reflect an issue of lowered abilities for neural activation in patients or to the possibility of reduced general neural processing abilities.

3.5 Effects of Middle Age on ERP Effects of Explicit Memory

Earlier analyses determined no observable differences between the young and mid-aged control groups for the implicit memory related ERP effects (section 3.2, footnote ⁴); however, existing ERP studies of memory and aging have suggested that ERPs of recognition in explicit memory can differ as a function of age (Duarte et al., 2006; Friedman, 2000, 2013; Nessler et al., 2008; Wang et al., 2012). Some of the control analyses that were performed included a larger sample of younger controls subjects (Figure 3, 4, 6), and though unlikely, it may still be possible that there could be differences among the groups as a function of age and that this could affect ERP effect magnitudes in ways that may not have been evident in the permutation analyses (Figure 3) or range-normalized topographic analysis (Figure 4). Therefore, for completeness and to account for this possibility, the raw magnitudes of the traditional ERP effects (FN400 and LPC; Addante et al., 2012a; Addante et al., 2012b; Leynes et al., 2005; Rugg et al., 1998; for reviews see (Curran, 2000; Friedman, 2000; Rugg and Curran, 2007)) were directly assessed between both groups in order to determine if, or to rule out that, there might be any evidence to support the possibility that age could be a factor in the present findings, instead of the neuropsychological factors.

⁸Author acknowledges an anonymous reviewer for noting this possibility.

For each ERP effect (differences between high and low confidence hits, FN400: from 400–600 msec at mid-frontal site Fc1, and LPC: from 600–900 msec at P3 site) (Addante et al., 2012a), raw amplitude voltages were entered into a 2×2 ANOVA with factors of condition ('old 5' vs. 'old 4') and group (young adult, mid-aged control). For the FN400, there was a significant effect of condition ($F(1,29) = 15.68, p < .001$) (Figure 6), but no condition by group interaction ($F(1,29) = 1.05, p = .461$); for the LPC there was a significant effect of condition ($F(1,29) = 26.58, p < .001$), and also no condition by group interaction ($F < 1$), indicating that for each effect high confidence hits were more positive going than low confidence hits in both control groups, and that each of the two ERP effects were equivalent in both groups (Mid-aged controls: FN400: $M = 1.42, SE = .50$, LPC: $M = 2.90, SE = .45$; Young controls: FN400: $M = 2.07, SE = .41$, LPC: $M = 2.82, SE = .53$). Therefore, there was no difference between groups in either ERP effects of FN400 or LPC (such as a possible graded attenuation in magnitude that might be presumed, (i.e.: Friedman, 2013; Wang et al., 2012), indicating that similar to implicit memory (results section 3.2, footnote 4), ERP effects of explicit memory are not affected by middle-aging, as opposed to findings of differences in more advanced years of aging. Together this finding indicates that ERP differences observed between groups for implicit memory could be reasonably attributed to the factor of neuropsychological patient group, and cannot be attributed to factors of age.

4.0 Discussion

4.1 Discussion of main findings

The current investigation studied ERPs of implicit memory in mild amnesia patients and healthy controls using an ERP comparison that eliminated declarative memory differences (section 2.8; Supplemental Figure 2; sections 3.1, 3.1.1, 3.1.2). Prior findings from this technique (Woodruff et al., 2006; Yu and Rugg, 2010) were first replicated in two independent control groups (Figure 4), which exhibited reliable implicit memory effects in posterior scalp regions that were consistent with similar findings of implicit memory from studies in several different laboratories (Galli et al., 2010; Groh-Bordin et al., 2006; Lucas and Paller, 2013; Rugg et al., 1998; Swaab et al., 2002; Woollams et al., 2008). However, patients were found to be impaired relative to the two groups of control subjects in a measure of implicit memory, as quantified by a reliable condition × group crossover interaction (Figure 1). Several control analysis were conducted to consider alternative factors that could account for the results, such as outlier subjects (Figure 1), sample size (Figure 3), age (Figure 6), the possible contamination by or inclusion of explicit memory (Figure 2), and the possible inability of patients to activate positive-going effects in posterior scalp region (Figure 5). Each of these alternatives was systematically ruled out. Implications of these findings are discussed below.

The neuropsychological results here converge with existing fMRI findings of implicit memory effects in the MTL that was attributed as outside of subject's conscious awareness (Daselaar et al., 2006b; Kirwan et al., 2009b), and also parallel the findings from other studies linking hippocampal activity to both unconscious processing of relational memories (Degonda et al., 2005; Hannula and Ranganath, 2009; Reber et al., 2012) and to related deficits in amnesia patients (Chun and Phelps, 1999; Hannula et al., 2007; for review see

Hannula and Greene, 2012). This has usually been interpreted as reflecting the properties of the hippocampus' role in these types of relational-binding computations for contextual and associative information (Degonda et al., 2005; Hannula and Greene, 2012; Reber et al., 2012), rather than reflecting a role of the hippocampus in fundamental forms of implicit memory processing. The current findings extend that assumption, since it provides evidence for a critical role of the human hippocampus in implicit memory processing for single items, and indicates that hippocampal patients are relying upon dramatically distinct neural systems for implicit memory processing than control subjects are. The current EEG data hence provides critical new insight into implicit memory processing in amnesia, and it qualifies the possibility that differences in implicit memory processing may actually be a common (though previously unidentified) component of amnesia that existing behavioral methods may have been insensitive to detecting (Berry et al., 2006; Berry et al., 2014; Berry et al., 2008a, b; Berry et al., 2012; Blaxton, 1992; Jernigan et al., 2001; Ostergaard, 1999).

While current results provide data that challenges traditional models of memory systems which were based upon neuropsychological findings excluding the hippocampus from a role in implicit memory (Eichenbaum et al., 2007; Gabrieli, 1998; Squire et al., 2007; Suthana and Fried, 2012), the results here are also consistent with a range of results from prior studies. For example, in addition to fMRI studies discussed above (Daselaar et al., 2006a; Kirwan et al., 2009a), amnesia patients such as Patient H.M. actually have been noted to exhibit certain implicit memory impairments, such as for repetition priming (Postle and Corkin, 1998; Xu and Corkin, 2001), but researchers considered that it was an idiosyncratic result (Corkin, 2002). The present findings provide evidence that deficits of implicit memory may be a more pervasive component of amnesia that future studies of memory systems should consider as perhaps a more fundamental – rather than idiosyncratic- part of memory. The current electrophysiological data is hence in line with existing neuropsychological findings (Chun and Phelps, 1999; Hannula et al., 2007; Postle and Corkin, 1998; Xu and Corkin, 2001) and neuroimaging results (Daselaar et al., 2006a; Degonda et al., 2005; Hannula and Ranganath, 2008, 2009; Kirwan et al., 2009a; Reber et al., 2012; Sheldon and Moscovitch, 2012)⁹, as well as theoretical models, discussed below.

4.2 Theoretical models

The current findings are consistent with existing models of memory that ascribe an early unconscious memory role to the hippocampus, such as the component process model (Moscovitch, 2008), which proposed that recollection may be a two-stage process that include an initial rapid assessment that is not consciously accessible, and a later second process that is slower and more deliberative. Consistent with current results, the early, unconscious process of the component process model was proposed to be hippocampally dependent, and it was proposed that indirect measures of memory would reveal deficits in memory inaccessible to consciousness (Moscovitch, 2008; Sheldon and Moscovitch, 2012;

⁹Relatedly, studies using intracranial EEG and fMRI have also similarly indicated a very early time course of hippocampal activity for memory, albeit related to explicit memory (Staresina et al., 2013; Staresina et al., 2012); and magnetoencephalography (MEG) studies have revealed an early physiological correlate of recognition (Jafarpour et al., 2014) which was found to also be impaired in a group of hippocampal patients as well (Horner et al., 2012). One possible implication from the current finding is that other physiological reports of early hippocampal signals for explicit memory may have also been reflecting a contribution of implicit memory, given the known propensity of implicit processing to contribute to explicit memory measures (see Voss et al., 2012).

Sheldon and Moscovitch, 2010)– each of which was the pattern of results observed here (Figure 1). As such, the current results are consistent with the suggestion that the computations of the hippocampus for explicit memory may be dependent upon earlier signals of implicit memory in order to successfully recollect. This signal would then be integrated into the subjective experience of recollection via cortical regions such as the posterior parietal cortex (Vilberg and Rugg, 2008; Yazar et al., 2014) where the LPC effect is often observed as a putative neural correlate (e.g.: Addante et al., 2012a; Addante et al., 2012b). Such a model of ‘primed recollection’ would be consistent with earlier claims that perceptual representation systems underlying priming could also operate as an input to episodic memory (Tulving and Schacter, 1990; see also Cermak, 1997; Reber, 2013).

4.3 Alternative considerations

One possible account of the data is that results may be consistent with single-systems models of memory, which propose that there are similar underlying components to both implicit and explicit memory systems (Berry et al., 2014; Berry et al., 2008b) that could each be reliant upon the same neural structures (such as the hippocampus, for example). However, the reliable topographic dissociations that were found between the physiology associated with implicit memory effects (Figure 1) and the explicit memory effects (FN400) occurring during the same time window (Figure 4) weighs considerably against this view. Such findings provide physiological evidence that the implicit and explicit memory ERP effects are comprised of distinct functional systems (Rugg and Coles, 1995; Wilding, 2006a). Hence, the current study provides clear neuropsychological evidence that implicit and explicit memory may rely upon the same neural structure (i.e. the hippocampus), but also preserves the view that they operate as distinct functional systems (e.g.: Hamann and Squire, 1997), and as such remain problematic for single system accounts (Berry et al., 2014; Berry et al., 2008a, b).

Another set of possible considerations of the current findings is that the item recognition task might have included some recollection of relational information about the source memory judgment that followed in the paradigm (Supplemental Figure 1), or that implicit memory effects could alternatively reflect item-related differences (‘item-selection effects’) ¹⁰. Indeed, item memory is not process-pure, and the hippocampus is widely known to support relational binding (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001; Eichenbaum et al., 2007; Hannula and Greene, 2012; Hannula et al., 2006; Ranganath, 2010). However, there are several reasons why it is likely that the current ERP effects represent item-based memory processing – as opposed to relational processing. First, prior studies have used the same analytic procedure (see section 2.8, Supplemental Figure 2) and found the same implicit memory results when using an item-only paradigm that did not include source memory or relational demands (Woodruff et al., 2006; Yu & Rugg, 2010; Figure 4). Second, the current study employed an item-only analysis (see section 2.8) that excluded explicit memory responses that would have reflected contributions of relational or source memory (Figure 2, section 3.1.1, 3.1.2), and the results again replicated the findings from prior studies that used an item-only paradigm (Woodruff et al., 2006; Yu & Rugg,

¹⁰Author thanks two anonymous reviewers for identifying these two points.

2010; Figure 4). This lends strong support to the notion that these findings reflect item-related memory processing, as opposed to relational source information. Lastly, item-related differences could also theoretically drive differences between old and new items based upon which trials had been randomly selected for analysis. However, providing strong evidence against this possibility is the consistent ERP effects evident throughout the several systematic control analyses (Figure 2, section 3.1.1, section 3.1.2) which included different subsets of trials but yielded the same results (Figure 4). Hence, item selection effects are considered unable to provide a sufficient account of the current findings.

4.4.1 Interpretations

The patients were considerably impaired in a physiological measure of implicit memory relative to the ERP effects seen consistently among several control groups and prior studies. A critical aspect of this finding is that the results rested upon a crossover interaction of the implicit memory effect, such that there was a new > old pattern in patients (Figure 1), and this interaction therefore provided clear evidence for a fundamental difference between patients and controls in processing implicit memory. This suggests that qualitatively different neural systems are engaged by patients than are engaged by control subjects when processing previously seen versus new items. However, precisely what this pattern of ERPs in patients necessarily reflects is not fully resolved by the available data. Accordingly, two different interpretations of this data are possible: one being that this measure of implicit memory was present in both groups but merely operating differently in the patients— who would be seen as processing implicit memory in substantially different ways than controls (but that the implicit memory process captured by this contrast remained nevertheless intact). On the other hand, an alternative interpretation is that patients were actually impaired in this measure of implicit memory, and that upon the absence of this effect, it revealed another underlying effect in the opposite direction. Neither of these accounts can be completely ruled out based upon the current data, but are each considered in further detail below.

According to the first view of qualitative differences, the current study's measure of implicit memory would be seen as being intact in patients, but the manner in which it manifests would be seen as being simply different than that in the controls (i.e. opposite polarity). In support of this view is that the negative ERP effect in patients resembles repetition suppression effects seen in other modalities (Buckner et al., 1995; Dobbins et al., 2004; Gotts et al., 2012a, b; Schacter et al., 2007; Wig et al., 2005). The challenge for this account, though, would be that it does not readily explain why patients would exhibit such a clear difference from the positive repetition effects that were consistently evident and established in several different groups of control subjects (Figure 4), without still having to rely upon noting that some form of normal implicit memory process is impaired. Hence this interpretation of qualitative differences cannot be fully discounted, but is considered limited in its ability to account for the fact that some factor nevertheless remains dramatically different between groups for implicit memory.

4.4.2 Interpretation of results as impairments

The alternative view is that the negative old-new effect in amnesic patients reflects a specific impairment in implicit memory, and that the absence of normal implicit memory effects reveals other underlying processing that remained as residual. Under this view, the negative old-new effects would be considered as corresponding to the relative fluency elicited by the stimuli, and would become evident when the normally-overlying positive effects of implicit memory are impaired as a function of the amnesic lesion. Fluency refers to the ease with which the physical representation of a stimulus is perceived upon re-presentation, and it is commonly thought that it is this ease in processing which leads subjects to attribute having experienced the information before (Cermak, 1997; Cermak et al., 1992; Jacoby and Dallas, 1981; Whittlesea, 2002; Whittlesea and Leboe, 2000; Whittlesea and Williams, 2000; Whittlesea and Leboe, 2003). Support for this alternative interpretation come from a convergence of electrophysiological and neuropsychological findings; the background research forming the basis for this perspective is discussed in further detail below.

Fluency is often found to be intact in amnesia patients amid other memory impairments (Conroy et al., 2005; Ozubko and Yonelinas, 2014; Verfaellie and Cermak, 1999), and amnesia patients have been known to specifically rely upon fluency-based processing when other processes fail (Cermak et al., 1992; Verfaellie and Treadwell, 1993). This has been interpreted as indicating that amnesia patients can respond based on fluency that is produced by low levels of automatic processing occurring during stimulus input (Cermak, 1997; Verfaellie and Treadwell, 1993), and that fluency can be evident in the absence of implicit knowledge (Dienes, 2011; Scott & Dienes, 2010). In healthy normal subjects, and using a shallow encoding paradigm that eliminated contributions of conscious recollection, Leynes & Zish (2012) reported negative-going ERP effects that corresponded to dissociable forms of both perceptual and repetition fluency. Similar to the current findings, those effects of fluency occurred early in time during an item recognition task, and had a posterior parietal topography, which paralleled similar findings for perceptual fluency reported by Voss & Paller (2010). Both of these prior studies suggested that the negative-going old-new effect was due to more fluent stimuli requiring less neural processing resources that led to the smaller amplitude for the 'old' condition relative to 'new', which is consistent with the current findings as well. Additionally, the patients' remaining ERPs correspond closely to the characteristics of the CNV readiness potential (see Results section 3.1) given the task requirement to sustain attention while preparing a motor response (all features common to a CNV (Leynes et al., 1998; Mento, 2013; Tecce, 1972; Walter et al., 1964).

Taken together, the patients' negative old-new effect can be seen as a secondary, underlying readiness potential that would ordinarily be masked by the overlapping primary ERP effects which are evident in controls (it is common for ERP components to overlap each other, c.f. Luck, 2005, 2014; Luck and Kappenman, 2012). From this view, that the patients' CNV potentials differentiated between 'new' and 'old' likely represents enhanced automatic perceptual and repetition fluency of the re-presented 'old' condition relative to 'new', given how closely they resemble the fluency effects identified by several other item recognition studies (Leynes and Zish, 2012; Voss and Paller, 2010). Relatedly, the positive-going ERP

effects of control subjects also corresponded closely with findings from other studies that have identified positive-going ERP differences for implicit memory corresponding to conceptual fluency (Kurilla and Gonsalves, 2012; Mecklinger et al., 2012; Nessler et al., 2005; Paller et al., 2007; Voss et al., 2012; Woollams et al., 2008).

One admittedly speculative possibility for future research is that the distinct positive and negative ERP effects evident in controls and patients may be corresponding to the different neural correlates of conceptual implicit memory and perceptual/repetition fluency, respectively (see Leynes & Zish (2012) for related discussion). If so, then it would be consistent with Cermak's (1997) proposal that the underlying processes which supports implicit memory may be substantially different in controls and patients, and that low-level automatic perceptual repetition fluency can be evident in the absence of other implicit processes (Cermak, 1997; Verfaellie and Treadwell, 1993). However, it is currently unknown how the implicit memory contrast used in the present study may be sensitive to differentiating between the myriad of processes comprising implicit memory (Richardson-Klavehn and Bjork, 1988; Vaidya et al., 1999; Voss et al., 2012; Westerman, 2008; Whittlesea, 2002). Hence, future research is needed to determine the extent to which it is sensitive to relative contributions of short term fluency from recent perceptual repetition (Leynes and Zish, 2012; Westerman, 2008) and/or other forms of more permanent influences in implicit memory.

4.5 Conclusions

To summarize, results from the crossover interaction of implicit memory effects between patients and control groups indicate that at least one of two possibilities are evident: either a) hippocampal damage fundamentally *changes* the way that implicit memory is being processed (possibly via re-organization or re-wiring that occurs after damage) and hence that the hippocampus is playing a *critical* role in normal implicit memory processing that is fundamentally disrupted after damage –but not eliminated-, or, b) that the hippocampus is *necessary* for this form of implicit memory processing and that the current patients are impaired in this implicit memory signal after their damage to this region. Available evidence supports the latter view, but since the current series of experiments are unable to fully adjudicate between these possibilities, future research is needed to better understand if this pattern of effects in patients represents an absence of an implicit memory process, or a re-organized change in how implicit memory is being achieved. Importantly, though, a conclusion common to each is that the hippocampus is invariably providing a critical role in a basic form of implicit memory processing.

In closing, there were several key findings revealed in the current study. In general, through a convergence of neuropsychological and electrophysiological methods and several independent experiments, the current study discovered that a group of amnesia patients with damage linked to the hippocampus exhibited clear physiological differences from normal control subjects in a basic form of implicit memory. Specifically, a neuropsychological dissociation was identified between electrophysiological activity for implicit and explicit memory, in which physiological correlates of implicit memory appear substantially impaired in mild amnesia patients relative to controls (Figure 1), despite equivalent physiological

correlates of explicit memory (FN400, (Addante et al., 2012a). As such, results provide key evidence to reveal that the hippocampus is critically involved in implicit memory, and not just as a function of its computational properties for binding relational, associative, or contextual information. This suggests that the hippocampus plays a more fundamental role than has usually be thought in aspects of memory processing that is beyond conscious awareness.

The hippocampus has traditionally been thought not to have a necessary role in basic implicit memory. The current findings present a challenge to this core assumption, and may represent increased sensitivity of both the relatively novel procedure used and the precision of EEG methods to detect such differences, as opposed to the behavioral methods usually used for studying implicit memory in amnesic patients. This adds to a growing body of work revealing a critical role of the hippocampus in implicit memory that occurs without awareness for associative, contextual, and relational binding, and specifically extends this role to single-item processing, as it appears that the hippocampus is also contributing to perhaps our most basic implicit experiences. Hence, results indicate that implicit and explicit memory systems may rely upon the same underlying neural structures – but function in different physiological ways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Implicit Memory Effects

Top panel: Raw voltage of the experimental contrast of interest, old vs. new items, which had each been equated for subjective responses of explicit memory (see Methods). Bottom: ERPs of posterior cluster of electrode sites for the old and new strength-equated conditions (see Methods), plotted for patients and controls. X-axes represent time in milliseconds after stimulus onset. Asterisk symbols indicate statistical significance levels for old-new effects in controls for the latencies indicated by horizontal lines ($p < .05 = *$, $p < .01 = **$). Right: Amplitude of effects for mean old-new differences from 400–600ms plotted for each individual subject, error bars represent standard error of the mean.

Confidence Levels Included in Old-New Implicit Memory Contrast

Figure 2. Implicit memory effects remain unaffected by inclusion and exclusion of high confidence responses

Topographic maps indicate the memory effects of old-new differences (see Methods, Figure 2), with warm colors indicating positive differences, and cool colors indicating negative differences. Top row: control subjects, asterisk symbols indicate statistical significance levels for old-new effects in controls ($p < .05 = *$, $p < .01 = **$, $p < .001 = ***$; † = marginal significance level $p < .10$). Bottom row: patients, asterisk symbols indicate significant effects of condition $\times$ group interactions between patients and control subjects. The first column represents the main effects reported in Figure 1, and is provided for comparison purposes to the subsequent columns' contrasts. In the first three columns, comparison of 'old' and 'new' items included the same confidence bins, whereas the final two columns contrast 'old' items to 'new' items that had included higher confidence levels of explicit memory responses (i.e. false alarms). Topographies are range-normalized to illustrate the peaks of effects, and voltage scales of each scalp map are indicated below.

Figure 3. Null distribution of t-values derived from non-parametric permutation test

Results represent t-values obtained from comparing implicit memory effects between two different groups sized $N=6$ and $N=3$, drawn randomly from the sample of $N=25$ subjects, and indicate resulting t-values from a between-subject t-test of their old-new differences (the computational equivalent of assessing a condition $\times$ group interaction). Critical t-values identified were -2.20 and 2.75 , whereas the observed t-value for the patients' impairment in implicit memory effects was 6.10 .

Figure 4. Topographies of ERP effects for explicit and implicit memory

All topographic maps are plotted for the latency of 400–600 msec. Top row: Difference waves for high and low confidence item recognition hits, representing the mid-frontal old-new effect, e.g.: “FN400”. The first column plots the preceding work of Yu & Rugg (2010) shown for comparison purposes (reproduced with permission. Note: in that study their latency was 300–500 msec, using a modified item confidence paradigm), followed by each of the current experimental control groups assessed topographically. The far right column illustrates effects in the patient group for comparison purposes. Bottom panel: the implicit memory measure of the current experiment. Topographies are range-normalized; hence warm colors represent relatively more positive values and cool colors more negative; minimum and maximum microvolt values for the range are provided beneath each plot.

Figure 5. ERP effects of confidence

Memory confidence judgments were collapsed across study status and accuracy, and compare the most confident responses to the remaining less confident responses, while holding memory constant. Top panel: topographies of confidence effects. Bottom panel: ERPs of confident and unconfident responses for control subjects and patients at a cluster of midline posterior electrode sites.

Difference Wave Amplitudes: High > Low Confidence Recognition Hits

Figure 6. The effects of middle age on the ERP correlates of recognition memory

Quantification of difference waves for memory effects serving as the putative correlates of familiarity and recollection, respectively. To provide context, data from patients are included for comparison purposes, whom were impaired on recollection but exhibited intact familiarity-related ERP effects of the FN400, parallel to the observed behavioral patterns.

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.

Table 1

Neuropsychological Profiles of Patients

Patient	Age (at time of test)	Education (years)	WAIS-R IQ	WMS-R Attention	WMS-R Verbal	WMS-R Visual	WMS-R General	WMS-R Delay
01	49	16	96	97	62	130	79	83
02	50	13	94	96	94	77	87	80
03	24	16	111	103	80	105	87	68

Table 2
Distributions of Item Recognition Responses for Patients, Controls, and Young Adults

Patients (N=3)	Sure new '1'	Unsure new '2'	Guess '3'	Unsure old '4'	Sure old '5'
Old Items	.02 (.01)	.20 (.16)	.14 (.03)	.29 (.06)	.35 (.16)
New Items	.10 (.06)	.40 (.32)	.17 (.10)	.21 (.14)	.12 (.16)
Age-matched 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)
Young Controls (N=25)					
Old Items	.04 (.05)	.10 (.05)	.08 (.05)	.24 (.11)	.53 (.16)
New Item	.33 (.17)	.35 (.13)	.15 (.10)	.14 (.09)	.04 (.03)