**The Impact of Depression on Brain Activity During Source Memory Retrieval**

Elyssa M. Barrick and Daniel G. Dillon

Number of words: 3,998

Number of figures: 6

Number of tables: 2

Supplemental information: stimulus list, map of electrode locations

Keywords: depression, memory, retrieval, ERP, source, recollection

Corresponding author:

Daniel G. Dillon, Ph.D.

Center for Depression, Anxiety and Stress Research

McLean Hospital

115 Mill Street, Belmont, MA 02478

Email: ddillon@mclean.harvard.edu

Phone: 617-855-4233

Fax: 617-855-4231

**Abstract**

**Background:** Recollection is disrupted in Major Depressive Disorder (MDD), but this disruption can be minimized by focused attention at encoding and retrieval. The neural mechanisms responsible for these clinically important phenomena are unclear. Thus, we used event-related potentials (ERPs) to examine recollection in MDD.

**Methods:** Twenty-four unmedicated adults with MDD and 24 controls encoded words shown on the left or right (perceptual source) by making animacy or mobility judgments (conceptual source). ERPs were recorded during cued source retrieval, which depends on recollection.

**Results:** At encoding, no group differences were observed but mobility judgments elicited slower responses than animacy judgments, suggesting deeper encoding. At retrieval, emory accuracy was characterized by a *Group* x *Cue* x *Encoding Task* interaction: depressed adults were generally less accurate and less confident than controls, but they showed excellent conceptual source memory following deeper encoding. In parallel, a positive parietal ERP deflection that tracks recollection was globally reduced in depression, but sustained left parietal activation was seen during conceptual source judgments for deeply encoded words in MDD.

**Conclusions:** This study links two reliable effects of depression on recollection to electrophysiological activity over parietal cortex. First, accuracy and confidence were reduced in MDD, and the most reliable ERP correlate of recollection—a positive parietal deflection from 400-800 ms—was blunted. Second, depressed adults showed excellent memory when the encoding and retrieval tasks demanded sustained attention, and this combination elicited slasting left parietal activity. These results link the impact of depression on recollection to parietal circuits that communicate with the hippocampus, highlighting the need for further work on this important topic.

**Introduction**

Memory retrieval plays a key role in Major Depressive Disorder (MDD) and, increasingly, in its treatment. Retrieval in depression is “overgeneral” (Williams et al., 2007): cued to recall specific episodes, depressed adults tend to offer categorical accounts, summaries that convey gist but few details. This lack of precision has consequences, as overgeneral retrieval predicts a longer course of illness (Brittlebank, Scott, Williams, & Ferrier, 1993; Peeters, Wessel, Merckelbach, & Boon-Vermeeren, 2002; Sumner, Griffith, & Mineka, 2010). Moreover, increasing retrieval specificity can decrease hopelessness and brooding rumination, improve problem solving, and lead to sustained remission (Neshat-Doost et al., 2012; Raes, Williams, & Hermans, 2009). In short, memory retrieval is impaired in depression and enhancing it can bring lasting relief.

Given these facts, the paucity of data regarding the neurobiology of memory retrieval in depression is astonishing, particularly since episodic retrieval in healthy adults has been studied extensively (Eichenbaum, Yonelinas, & Ranganath, 2007; Rugg & Curran, 2007; Rugg & Vilberg, 2013). This does not reflect lack of desire; a decade ago, the National Institutes of Mental Health, Aging, and Neurological Disorders and Stroke called for integrated research on depression and memory (Steffens et al., 2006). Furthermore, the nature of the problem is clear. As one might expect from work on overgeneral memory, depression impairs recollection—the retrieval of contextual details specifying the spatiotemporal source of memories (G M MacQueen, Galway, Hay, Young, & Joffe, 2002; Glenda M MacQueen et al., 2003; Raes et al., 2006; Ramponi, Barnard, & Nimmo‐Smith, 2004). However, despite dozens of event-related potential (ERP) and functional magnetic resonance imaging (fMRI) studies of recollection in healthy adults, no similar literature in MDD has emerged.

The current study addresses this gap by using ERPs to study source memory in MDD. We adapted a design that dissociates neural systems engaged by conceptual versus perceptual source retrieval (Bergström, Henson, Taylor, & Simons, 2013; Dobbins & Wagner, 2005; Simons et al., 2005), using neutral stimuli to avoid confounds associated with mood-congruent encoding (G H Bower, 1981; Gordon H. Bower, 1987; Dillon, Dobbins, & Pizzagalli, 2014). At study, participants viewed words presented on the left or right above a question specifying either an animacy or mobility judgment. At test, they were cued to retrieve the presentation side (perceptual source) and encoding task (conceptual source).

A recent fMRI/ERP study (Bergström et al., 2013) found that both conceptual and perceptual retrieval elicited the most well-studied ERP marker of recollection: a positive deflection over parietal cortex that extends from about 400-800 ms post-stimulus, often with a left hemisphere maximum, and that is thought to reflect information transfer between the hippocampus and parietal lobes (Rugg & Curran, 2007). Both forms of retrieval also activated the precuneus and elicited a negative polarity ERP maximal over posterior electrodes and referred to as the late posterior negativity, or LPN (Cycowicz, Friedman, & Snodgrass, 2001; Johansson & Mecklinger, 2003; Mecklinger, Johansson, Parra, & Hanslmayr, 2007). The LPN extended over left frontal cortex during conceptual retrieval, and this was mirrored by fMRI activation in the dorsolateral PFC.

These findings suggest that retrieval attempts activate parieto-hippocampal circuits, bringing candidate memories to mind and generating the parietal ERP effect. Next, those candidate memories are reviewed until one is selected and endorsed. The review and selection of perceptual memories strongly engages posterior cortical regions, but conceptual retrieval differentially activates left PFC regions that support semantic encoding, elaboration, and selection (Badre & Wagner, 2007). Because MDD is associated with volumetric loses in hippocampus and PFC (Treadway et al., 2015), and because depressive rumination may occupy left PFC circuits, we anticipated disrupted conceptual source memory in depression.

However, during our analysis it became clear that we had overlooked a key factor. Specifically, several studies report good memory in depression provided attention is sustained at encoding or retrieval (P. T. Hertel & Brozovich, 2010; P.T. Hertel & Rude, 1991; Paula T. Hertel, 1997; Paula T. Hertel, Benbow, & Geraerts, 2012; Paula T. Hertel & Hardin, 1990). As detailed below, one of our tasks promoted deeper encoding than the other, and when words from that task were targeted for conceptual source retrieval, the MDD group was quite accurate. Thus, this study highlights neural mechanisms linked to disrupted source memory in MDD, as well as activity that supports recollection when encoding and retrieval conditions are salubrious.

**Materials and Methods**

**Participants and self-report**

Participants (18-62 years old, right-handed, no neurological or unstable medical conditions) were recruited from the community and compensated ($25/hour), using a protocol approved by the Partners HealthCare Human Research Committee. They were screened by phone or online, and we assessed psychiatric history with the MINI International Neuropsychiatric Interview, version 6.0 (Sheehan et al., 1998), also administering the Beck Depression Inventory II (BDI; Beck, Steer, & Brown, 1996). Controls had to report no current or past psychiatric conditions. Depressed adults had to report current depression, no history of other DSM-IV Axis I diagnosis (except generalized anxiety, social anxiety, or specific phobia secondary to MDD), no medication use in the past two weeks (six weeks for fluoxetine, six months for neuroleptics), and a BDI-II score ≥ 14. Thirty-four controls and 26 depressed adults completed the ERP session. Data from 10 controls and 2 depressed adults were excluded due to excessive artifacts (see below), leaving 24 individuals per group.

We also administered the Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1995), the Ruminative Responses Scale (RRS; Treynor, Gonzalez, & Nolen-hoeksema, 2003), and the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). These probe symptoms of depression and anxiety, trait rumination, and sleep quality over the last month, respectively. The MASQ and RRS are commonly used in work with depressed participants as these assess core cognitive and affective aspects of depression, with the MASQ also providing insight into anxiety. The PSQI is used less frequently but was included because sleep has beneficial effects on human episodic memory (Plihal & Born, 1997) and there is now a substantial body of evidence linking depression and other psychiatric disorders to sleep disruption (Deldin, Phillips, & Thomas, 2006; Wulff, Gatti, Wettstein, & Foster, 2010). Thus, we expected to find negative relationships between these measures on the one hand and both memory accuracy and ERP indices of successful source retrieval on the other. Finally, the Wechsler Test of Adult Reading (WTAR; Holdnack, 2001) was used to assess IQ. One control did not complete the MASQ and one depressed participant did not complete the PSQI.

**Task**

The task was programmed in PsychoPy (Peirce, 2008). Due to a hardware change, RT data were not recorded for one control and one depressed participant.

**Stimuli.** We used the MRC Psycholinguistic Database (Coltheart, 1981) to select 25 words from four categories: “living/immobile” (e.g., *oak*), “non-living/immobile” (e.g., *shed*), “living/mobile” (e.g., *dog*), and “non-living/mobile” (e.g., *kite*). ANOVA yielded no differences for number of letters (mean±S.D.; 5.27±1.29) or syllables (1.52±0.50), frequency (35.58±79.02), concreteness (598.87±20.18), or imageability (596.80±25.31), *ps* > 0.064. Words are listed in the Supplement.

**Encoding.** The task included six encoding-retrieval cycles. Each encoding block included 16 trials (Figure 1, *left*) in which a word appeared on the left or right above one of two questions: “living/non-living?” or “mobile/immobile?” Participants responded by pressing a button. A jittered interval (500-2000 ms) separated the trials.

**Counting.** Immediately after encoding, a 3-digit number (e.g., 931) was shown and participants counted backwards from that number in steps of three for 30 s. Counting served to disrupt rehearsal and clear working memory (Reitman, Higman, Lifson, & Rosenblum, 1974).

[PLEASE INSERT FIGURE 1 ABOUT HERE]

**Retrieval.** Each block comprised 48 trials that included a cue, word, and response screen (Figure 1, *right*). On 16 trials each, the cue was “Side” or “Question” and the word came from the preceding encoding block; these cues prompted perceptual and conceptual source retrieval, respectively. On the remaining trials the cue was “Odd/Even” the word was a numeral between “one” and “ninety-six”, and the participant judged parity. All trials involved reading a cue, interpreting it, and retrieving information, but on Odd/Even trials retrieval was directed at semantic rather than episodic memory. Thus, comparing ERP data from Side or Question trials versus Odd/Even trials should isolate activity mediating episodic retrieval. Presentation order of words and cues was random. The response screen consisted of ‘RESPOND’ printed above the word with the numbers 1-5 printed below and corresponding to a choice and level of confidence (Figure 1, *right*). As in other studies of source memory (Starns & Hicks, 2005), “guess” was included as a response option. Participants were instructed to select this option when they felt they could not recover any information favoring one source over the other, which should minimize the contribution of guessing to successful retrieval (i.e., an analysis focused on hits should not be contaminated with guesses). A jittered interval (500-2000 ms) separated the trials.

**EEG Recording**

The EEG was recorded during retrieval with a 128-sensor HydroCel GSN Electrical Geodesics Inc (EGI) net (sample rate: 1000 Hz, 0.02–100 Hz). Data were referenced to vertex and impedances were kept below 45 kΩ when possible (maximum: 75 kΩ).

**Behavioral Analysis**

The behavioral data were cleaned by dropping trials with no response or where RT exceeded the participant’s mean±3SD (< 1% of encoding trials, < 2% of retrieval trials). The behavior analysis involved *t*-tests andmixed-model Type III ANOVAs implemented in the R software (R Developement Core Team, 2015) library *afex* (Singmann, Bolker, Westfall, & Aust, 2016). For both encoding and retrieval, accuracy was computed as percent correct. At encoding, *Group* x *Task* (mobility, animacy) x *Side* ANOVAs were run for accuracy and correct RT. At retrieval, *t­*-tests were first used to compare accuracy, confidence, and correct RT on Odd/Even trials, as it was important to ensure there were no group differences in this control condition. Next, a *Group* x *Cue* x *Task* (mobility, animacy) ANOVA was run on the number of “guess” responses in each condition to determine whether the MDD group guessed more often than the controls did. Finally, responses on Question and Side trials were analyzed by running *Group* x *Cue* x *Task* ANOVAs for accuracy, confidence, and correct RT. Alpha was set at 0.05.

**ERP Analysis**

**Pre-processing.** Pre-processing was conducted with EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) toolboxes for MATLAB (MathWorks, Natick). EEG data were merged, re-referenced to the average of all electrodes, and filtered (0.1-30 Hz). Bad channels were interpolated, independent components analysis was used to remove activity reflecting blinks, HEOG, and EKG, and the cleaned data were time-locked to word onsets and segmented (-200 to 2000 ms). The pre-stimulus interval was used for baseline correction, and segments where any raw value or the maximum-minimum voltage difference (200 ms intervals, 100 ms sliding window) exceeded 100 μV were rejected. We used *a priori* criteria of > 18 bad channels or more than 50% of trials rejected to exclude datasets (10 controls, 2 MDD). The mean number of clean segments in each bin defined by *Group* x *Cue* x *Task* ranged from 21-28 for source hits.Guesses were excluded from ERP analysis and there were too few clean segments for analysis of misses. Thus, the analysis was focused on correct responses (hits), a commonly used approach in this literature (Bergström et al., 2013; Dobbins & Wagner, 2005; Han, Oʼconnor, Eslick, & Dobbins, n.d.).

**Group-level analyses**. In our first group level analysis, we computed “Question minus Odd/Even” and “Side minus Odd/Even” difference waves to isolate activity tracking conceptual and perceptual source retrieval, respectively, closely following prior methods (Bergström et al., 2013) and testing our *a priori* hypothesis, which was that the MDD group would show a selective deficit for conceptual (but not perceptual) retrieval. The second analysis was intended to parallel the memory accuracy data, which were characterized by a *Group* x *Cue* interaction for words from the mobility task but not the animacy task. To identify activity mediating this interaction, we computed “Question minus Side” difference waves separately for words from each encoding task in each group. For both analyses, we submitted the difference waves to mass univariate analysis (Groppe, Urbach, & Kutas, 2011a), focusing on mean amplitudes from 400-800 ms, 800-1400 ms, and 1400-2000 ms. These windows were chosen because the 400-800 ms interval should capture the left parietal effect most consistently associated with recollection (Rugg & Curran, 2007), and the latter two windows should capture (a) a long-lasting late positivity frequently observed over right frontal cortex in recollection experiments (Wilding & Rugg, 1996), (b) a late posterior negativity (LPN) consistently seen during source recollection (Johansson & Mecklinger, 2003), and (c) a separate late negativity prominent over left frontal scalp regions during conceptual retrieval (Bergström et al., 2013).

Mass univariate analysis is widely used in fMRI research (Friston et al., 1995) and here entails a one-sample *t*-test (within-group analysis) or a two-sample *t*-test (between-group analysis) at each electrode. By examining every electrode and multiple time windows, this makes better use of the spatiotemporal richness of ERP data than traditional methods. To correct for multiple comparisons, we used cluster-based permutation (Groppe, Urbach, & Kutas, 2011b). All electrodes within 4 cm of each other were considered neighbors, and neighboring electrodes significant at *p* < 0.05 (uncorrected) were considered clusters. The use of a 4 cm inter-electrode distance reflects the fact that the mean distance between electrodes is about 3 cm on the 128 channel EGI net (Song et al., 2015): 4 cm is broad enough to detect clustered activity in regions where electrodes are relatively widely spaced (e.g., over parietal cortex) without being so broad as to detect false clusters. The sum of all *p*-values in a cluster constituted its mass. We then performed 2500 permutations, selecting the most extreme cluster mass from each permutation to generate a distribution (Bullmore et al., 1999) for judging the probability of observing clusters of various sizes. Only clusters significant at *p* < 0.05 (corrected) are reported.

**Individual Differences**

Within the depressed group, we used Pearson correlations to examine relationships between source memory accuracy, left parietal ERPs associated with recollection, and individual differences in sleep quality, the severity of depressive and anxious symptoms, and the extent of brooding rumination.

**Results**

**Demographics**

There were no group differences in gender, age, education, or estimated IQ (Table 1). Relative to controls, the MDD group endorsed poorer sleep, more rumination, and more symptoms of depression and anxiety, with the mean BDI-II score indicating moderate depression.

[PLEASE INSERT TABLE 1 ABOUT HERE]

**Behavior**

**Encoding**. The encoding data are presented in Figure 2. For response accuracy (Figure 2A), the only significant result was a main effect of *Task*, *F*(1, 46) = 12.70, *p* < 0.001, *d* = 0.46, reflecting lower accuracy for mobility versus animacy judgments. Neither the main effect of *Group* nor any interaction involving this factor approached significance, *F*s < 1. For correct RT (Figure 2B), the main effect of *Task* was again significant, *F*(1, 44) = 54.34, *p* < 0.001, *d* = 0.30, with slower responses for mobility versus animacy judgments. The RT analysis also revealed a *Group* x *Task* x *Side* interaction, *F*(1, 44) = 6.40, *p* = 0.015, but separate ANOVAs for words presented on the left and right did not reveal significant *Group* x *Task* interactions, *F*s < 3.69, *p*s > 0.05. As shown in Figure 2B, the 3-way interaction reflects the fact that while RTs were numerically shorter in the MDD group in all conditions, this difference was more pronounced for the animacy task for words presented on the left, and for the mobility task for words presented on the right. In summary, the mobility task was more difficult than the animacy task, as judged by lower response accuracy and slower RTs, and there were no reliable group differences.

[PLEASE INSERT FIGURE 2 ABOUT HERE]

**Retrieval: Odd/Even trials**. There were no group differences on Odd/Even trials, which were characterized by extremely high accuracy (controls: 98.42±3.96%; MDD: 99.13±1.36%; *t*(46) = -0.83, *p* = 0.41), fast correct RTs (controls: 859.87±299.18 ms; MDD: 777.22±225.65 ms; *t*(44) = 1.06, *p* = 0.30), and highly confident responses (percentage of high confidence Odd/Even trials: controls: 99.69±0.65%; MDD: 99.87±0.35%; *t*(46) = -1.16, *p* = 0.25).

**Retrieval: guessing**. Five participants (two controls, three MDD) never guessed and a further 15 participants (ten controls, five MDD) did not guess in at least one cell of the design. The remaining 11 controls and 17 depressed participants guessed at least once in every cell of the design; their data are shown in Figure 3, and they were included in the *Group* x *Cue* x *Task* ANOVA (because no participant guessed on an Odd/Even trial, this condition was omitted). The ANOVA revealed a main effect of *Cue*, *F*(1, 26) = 7.11, *p* = 0.01, reflecting fewer guesses under the Question cue versus the Side cue, and a main effect of *Task*, *F*(1, 26) = 12.34, *p* = 0.002, reflecting fewer guesses in response to words from the mobility task versus the animacy task.

[PLEASE INSERT FIGURE 3 ABOUT HERE]

Neither the main effect of *Group* nor any interactions involving *Group* were significant, *F*s < 1.83, *p*s > 0.18. However, inspection of Figure 3 suggested that, for words from the mobility task, the effect of cue type on guessing was pronounced in the MDD group. Indeed, a *t*-test confirmed that, for the mobility task, depressed participants guessed less frequently under the Question cue versus the Side cue, *t*(16) = -3.11, *p* = 0.007, *d* = 0.51, but this cue effect was not reliable for words from the animacy task considered alone, *t*(16) = -1.29, *p* = 0.22. Furthermore, there was no reliable effect of cue on guessing for words from either encoding task considered alone in the controls (*t*s < 1.33, *p*s > 0.21). Moreover, in the MDD group, words from the mobility task presented under the Question cue elicited fewer guesses than words from the animacy task shown under the Question cue, *t*(16) = -3.00, *p* = 0.008, *d* = 0.38, or words from the animacy task shown under the Side cue, *t*(16) = -3.09, *p* = 0.007, *d* = 0.75. In summary, across all participants guessed less in response to words from the mobility task versus the animacy task, and in response to the Question cue versus the Side cue. In the MDD group, the combination of these two factors (words from the mobility task presented under the Question cue) led to significantly fewer guesses than what was observed in the other cells of the design.

**Retrieval: source accuracy**. The source accuracy data are shown in Figure 4A. These data yielded main effects of *Cue*, *F*(1, 46) = 14.47, *p* < 0.001 and *Task*, *F*(1, 46) = 31.95, *p* < 0.001, as well as significant *Group* x *Cue*, *F*(1, 46) = 6.42, *p* = 0.01 and *Cue* x *Task*, *F*(1, 46) = 22.35, *p* < 0.001 interactions. The *Group* x *Cue* x *Task* interaction was not significant, *F* < 1, but there was a significant *Group* x *Cue* interaction for words from the mobility task, *F*(1, 46) = 6.45, *p* = 0.01, but not the animacy task, *F* < 1.The nature of this difference is illustrated in Figure 4B. For the depressed group, the mean Question minus Side accuracy difference score was positive for words from the mobility task but negative for words from the animacy task, and this difference was significant, *t*(23) = 3.82, *p* = 0.001, *d* = 0.78. By contrast, for controls the mean Question minus Side accuracy difference score was negative for words from both the mobility task and the animacy task, although the difference between these two was also significant, *t*(23) = 2.83, *p* = 0.01, *d* = 0.58. Critically, between-groups *t*-tests revealed more positive Question minus Side accuracy difference scores in depressed versus healthy controls for words from the mobility task, *t*(46) = 2.54, *p* = 0.015, *d*  = 0.73, but not the animacy task, *t*(46) = 1.00, *p* = 0.32, *d* = 0.29. Finally, the Question minus Side difference score for the mobility task was greater than zero in the MDD group, *t*(23) = 2.06, *p* = 0.051, but not the controls, *t*(23) = -1.49, *p* = 0.15.

[PLEASE INSERT FIGURE 4 ABOUT HERE]

In summary, the cue effect on accuracy was stable across groups for words from the animacy task (lower accuracy under the Question versus the Side cue, Figure 4B right panel), but it varied by group for words from the mobility task: depressed adults showed better source accuracy under the Question cue versus the Side cue, but accuracy did not vary reliably by cue in the controls (Figure 4B left panel).

**Retrieval: source confidence**. Figure 5A shows the confidence data. These were characterized by a main effect of *Task*, *F*(1, 46) = 6.72, *p* = 0.01, reflecting higher confidence in response to words from the mobility versus animacy task, *t*(47) = 2.75, *p* = 0.008, *d* = 0.13, as well as a main effect of *Cue*, *F*(1, 46) = 26.10, *p* < 0.001, that was qualified by a *Group* x *Cue* interaction, *F*(1, 46) = 4.37, *p* = 0.04. The interaction emerged because although there was no group difference in the percentage of high confidence responses under the Question cue, *t*(46) *<* 1, the depressed adults were less confident than controls in response to the Side cue, *t*(46) = 2.25, *p* = 0.03, *d* = 0.65. Finally, we conducted exploratory *t*-tests to confirm that, in the MDD group, confidence was higher under the Question versus Side cue for both the animacy task, *t*(23) = 4.35, *p* < 0.001, *d* = 1.01, and the mobility task, *t*(23) = 5.46, *p* < 0.001, *d* = 1.10. Thus, the effect of cue type on confidence did not vary by encoding task in the MDD group. This contrasts with the accuracy and guessing data, where the difference between responses to the Question versus Side cue was magnified for words from the mobility task (not the animacy task) in the MDD group.

[PLEASE INSERT FIGURE 5 ABOUT HERE]

**Retrieval: RT**. RT data from correct trials are shown in Figure 5B. The only significant effect was a main effect of *Cue*, with slower responses to the Question cue versus the Side cue, *F*(1, 44) = 194.99, *p* < 0.001, *d* = 1.53. The effect of *Group* was not significant, *F* <1, and neither were any interactions with *Group*, *F*s < 2.89, *p*s > 0.09.

**Overall behavioral summary**. At encoding, mobility judgments were made more slowly and less accurately than animacy judgments. This appears to have supported better retrieval as both groups guessed less and were more confident when responding to words from the mobility task. Furthermore, participants responded more slowly, guessed less, and were more confident under the Question versus the Side cue. Importantly, the combination of words from the mobility task presented under the Question cue yielded improved performance in the MDD group. Depressed participants guessed least frequently in this cell of the design, and source accuracy for words from the mobility task was characterized by a *Group* x *Cue* interaction: in depressed adults, accuracy was better under the Question cue versus the Side cue, an effect that was not seen in the controls. This pattern differed from that observed with words from the animacy task, where both groups were less accurate under the Question cue versus the Side cue. It also differed from the pattern seen for confidence, where the MDD group was less confident than controls when making Side judgments for words from either encoding task. In short, the mobility task and Question cue led to few guesses and supported confident responding in all participants, and the interaction of these two factors boosted accuracy in the MDD group.

**ERPs**

**Conceptual and perceptual retrieval, collapsed over encoding task**.To test our *a priori* hypothesis, we conducted between-group tests on “Question minus Odd/Even” and “Side minus Odd/Even” difference waves, collapsed across encoding task as in several prior studies. We expected group differences in the former but not the latter contrast, but in fact we found no significant group differences in either contrast (smallest cluster *p* = 0.29). Thus, we present the contrasts collapsed across the groups in Figures 6 and 7.

[PLEASE INSERT FIGURE 6 AND TABLE 2 ABOUT HERE]

Figure 6 shows the “Question minus Odd/Even” contrast and Table 2 lists the electrodes where significant differences were observed. As shown in the top panel of the figure, from 400-800 ms there were two clusters of differential activity. As expected, Question hits elicited more positive ERPs than Odd/Even hits over left parietal electrodes, consistent with many prior studies of recollection (Rugg & Curran, 2007). In addition, there was a relative negativity for Question hits versus Odd/Even hits over right frontal electrodes in this time window. As shown in the middle and bottom panels of the figure, later intervals (800-1400 ms and 1400-2000 ms) were characterized by sustained negative polarity potentials for Question hits relative to Odd/Even hits over left frontal and right occipital sites. The left frontal result replicates a recent study that linked this potential specifically to conceptual retrieval (Bergström et al., 2013), while the lasting late posterior negativity (LPN) has been observed in studies of both conceptual and perceptual source memory (Bergström et al., 2013; Johansson & Mecklinger, 2003; Mecklinger et al., 2007). This pattern of results is quite consistent with prior work, but—again—we saw no group differences in this contrast.

There were also no group differences for the “Side minus Odd/Even” contrast, which was designed to probe perceptual retrieval and is shown in Figure 7 (see Table 3 for a list of electrodes that showed reliable effects of condition). Mass univariate analysis conducted across the groups revealed no differences between the conditions from 400-800 ms. However, strong condition effects were observed from 800-1400 ms and 1400-2000 ms. In these windows, a sustained LPN was seen over the posterior midline, from anterior parietal to occipital sites.

***Question* minus *Side*, animacy task**. The retrieval cues strongly affected source accuracy for words from the animacy task, with worse performance under the Question cue relative to the Side cue seen in both groups (Figure 4A, right panel). To probe the neural correlates of this effect, we computed “Question minus Side” difference waves for words from the animacy task. A between-groups test revealed no reliable differences (smallest cluster *p* = 0.20), thus we present data collapsed across groups in Figure 8 (also see Table 4). As shown, this contrast revealed a broadly distributed negativity that was focused over left fronto-central scalp from 400-800 ms, dispersed over bilateral fronto-central scalp from 800-1400 ms, and separated into left fronto-central and right parietal clusters from 1400-2000 ms. Inspection of waveforms revealed a consistent pattern: relative to Side hits, Question hits elicited more negative potentials, with below-baseline activity especially evident over left fronto-central scalp.

[PLEASE INSERT FIGURE 8 AND TABLE 4 ABOUT HERE]

***Question* minus *Side*, mobility task**. Finally, we computed “Question minus Side” difference scores for words for the mobility task and compared responses across the two groups. As shown in Figure 9 (see also Table 5), this contrast was associated with group differences over left centro-parietal scalp between 400-800 ms (Figure 9, top) and 800-1400 ms (Figure 9, middle). In these intervals, the depressed and healthy groups generated similar responses for Question hits, but the depressed group showed a much weaker response for Side hits. Indeed, follow-up *Group* x *Cue* ANOVAs on mean amplitudes averaged over all electrodes in these clusters (Figure 9, bottom) revealed significant interactions in both windows (*F*s > 14, *p*s < 0.001). These reflected significant control > MDD effects for Side hits (*t*s > 2.2, *p*s < 0.025), but not Question hits (*t*s < 0.7, *p*s > 0.52). Moreover, the MDD group generated stronger responses on Question versus Side hits in both time windows (*t*s > 3.1, *p*s < 0.006), but controls showed the opposite pattern—stronger responses to Side versus Question hits (*t*s > 2.0, *ps* < 0.056). This pattern of ERP effects is quite similar to the pattern seen for source accuracy (Figure 4).

[PLEASE INSERT FIGURE 9 AND TABLE 5 ABOUT HERE]

**Individual Differences**

To look for brain/behavior relationships across the groups, we first computed the mean amplitude of the left centro-parietal “Question minus Side” ERP difference waves for words from the mobility task from 400-800 ms and 800-1400 ms, averaging over the electrodes that showed group differences in the top and middle panels of Figure 9, respectively. The amplitude of the “Question minus Side” ERPs in these intervals were highly correlated, *r* = 0.84, *p* < 0.001. These values were also positively correlated with “Question minus Side” accuracy difference scores, although the relationships were not very strong (correlation with accuracy: 400-800 ms, *r* = 0.18, *p* = 0.21; 800-1400 ms, *r* = 0.28, *p* = 0.05).

Next, we considered individual differences in the depressed adults considered alone, again focusing on “Question minus Side” comparisons for words from the mobility task. First we computed Pearson correlations to determine if there was any association between “Question minus Side” accuracy for words from the mobility task and depressive severity (BDI-II total), anhedonia (MASQ-AD), general distress associated with anxiety (MASQ-GDA), anxious arousal (MASQ-AA), brooding rumination (RRS-Brooding), or sleep disruption (PSQI total). We found negative relationships between source accuracy and both general anxiety (Figure 10A; *r* = -0.42, *p* = 0.04) and anxious arousal (Figure 10B; *r* = -0.47, *p* = 0.02); no other relationships were significant.

Next we examined relationships with ERPs from the “Question minus Side” contrast, computed for words from the mobility task. To maximize sensitivity, we did not restrict our analysis to sites that showed between-groups differences in this contrast (Figure 9), but instead extracted data from electrodes that showed significant effects when the MDD group was considered alone (Figure 10C). These electrodes were predominantly located over left centro-parietal scalp but they were more numerous than the electrodes that emerged from the between-groups analysis, and they showed significant effects of condition in all three time windows (400-800 ms, 800-1400 ms, 1400-2000 ms). The mean amplitude of ERPs from these electrodes was correlated across the time windows (*r*s > 0.39, *p*s < 0.053), but we did not find a relationship between source accuracy and ERP amplitude in any of these intervals (|*r*|s < 0.33, *p*s > 0.12). Moreover, the ERPs were not reliably related to any self-report measure with one exception: there were negative relationships between the PSQI score and ERP amplitude from 400-800 ms (Figure 10D; *r* = -0.48, *p* = 0.02) and 800-1400 ms (Figure 10E; *r* = -0.50, *p* < 0.02).

To confirm that this last result did not simply reflect depressive severity, we computed hierarchical regressions with ERP amplitude as the criterion, entering BDI-II and PSQI scores in steps 1 and 2. PSQI predicted ERP amplitude after accounting for BDI-II (400-800 ms; β = -0.45, *p* = 0.03; 800-1400 ms; β = -0.49, *p* = 0.03), and adding PSQI improved both models (Δ*R*2s > 0.16, Δ*F*s > 4.5, *p*s < 0.05). Thus, “Question minus Side” ERP amplitude for words from the mobility task was lowest in those depressed adults who reported chronic sleep disruption, and this effect was not driven by depressive severity.

[PLEASE INSERT FIGURE 10 ABOUT HERE]

**Discussion**

This study yielded two sets of behavioral and ERP findings. Relative to controls, depressed adults were less accurate and less confident in their memories, and they showed reduced parietal ERP amplitude from 400-800 ms. The negative effect of MDD on memory was modest, but in addition to reporting lower confidence than controls in all four cells of the design, the depressed adults were numerically less accurate in three cells. Worse performance in 7/8 cells is improbable under the null (binomial test, *p* = 0.035 one-tailed), thus recollection and brain activity indexing recollection were weaker in MDD.

However, depressed adults showed excellent memory for words from the mobility task presented under the Question cue, which we interpret as reflecting sustained attention. At encoding, the mobility task elicited longer RTs and lower accuracy than the animacy task. It is easy to see why—for example, because trees sway in the breeze, deciding whether *oak* is “mobile” is harder than deciding whether an oak is alive—and we think the additional consideration needed to render mobility judgments led to deeper encoding. At retrieval, the Question cue elicited longer RTs and more confident responses than the Side cue, suggesting more extended and successful memory searches. Thus, directing conceptual retrieval at words from the mobility task pairs a deep retrieval search with deep encoding. Depressed adults can perform well under these conditions (P.T. Hertel & Rude, 1991; Paula T. Hertel & Hardin, 1990), and our ERP data highlight a candidate neural mechanism: sustained recruitment of left parietal cortex, which was otherwise hypoactive.

We speculate that this ERP effect may track relatively effortless recovery of episodic details, because left parietal activity was not observed when words from the animacy task were presented under the Question cue; instead lasting activity over left PFC was seen. Animacy decisions were made quickly at encoding, consistent with shallower encoding in this condition, and accuracy under the Question cue was lower following the animacy versus mobility task (Figure 2A, right). Therefore, the left PFC activity may reflect additional cue elaboration needed to generate candidate memories following relatively poor encoding, or possibly post-retrieval monitoring or selection. Interestingly, the only other imaging study of source memory in MDD we know of reported increased left frontal activation during recollection attempts in depressed adults (Van Eijndhoven et al., 2013). That study did not manipulate encoding difficulty, but we predict that left PFC activation during source retrieval in MDD will be strongest when encoding is shallowest and recollection is weakest.

Our data may have treatment implications. As described earlier, imprecise retrieval is associated with depression and enhancing retrieval can speed recovery. Consideration of treatment mechanisms suggests an explanation. During cognitive behavioral therapy (CBT), patients recall difficult episodes from their lives and then reappraise them to reduce distress; here the importance of accurate retrieval is self-evident. But patients are also asked to imagine similar situations unfolding in the future so they can envision themselves effectively using new coping skills (Holmes, Arntz, & Smucker, 2007). Imagining future events depends on the same parieto-hippocampal circuitry that supports retrieval (Madore, Szpunar, Addis, & Schacter, 2016), and we have shown that activity in these circuits is blunted in MDD but can recover with adequate support. By extension, we speculate that effective CBT may be associated with improved functioning in parieto-hippocampal circuits. Given links between antidepressant effects and both functional and structural changes in the hippocampus (Santarelli et al., 2003), this argument may extend to psychopharmacological interventions as well. Finally, we expect that a sleep intervention would enhance memory retrieval in MDD, based on the negative relationship between sleep quality and ERP amplitudes observed in Figure 6.

In summary, this study provides novel insight into the impact of depression on brain activity during retrieval. The central role of parieto-hippocampal activity in episodic memory is already well-known. These data indicate that the same circuitry may play an important but underappreciated part in depression and its treatment.

**Acknowledgements**

The study was supported by NIMH grant R00 MH094438-03 (D.G.D) and by generous funding from McLean Hospital. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors gratefully acknowledge Victoria Lawlor for assistance with recruitment and participant testing, and Dr. Diego Pizzagalli for helpful comments on a draft of the manuscript.

**Financial Disclosures**

Dr. Dillon has received consulting fees from Pfizer, Inc., for work unrelated to this project. Ms. Barrick reports no biomedical financial interests or potential conflicts of interest.

**References**

**Figure Captions**

*Figure 1*. Encoding (left) and recognition (right) trial structures. Encoding trials began with three centrally presented arrows pointing to the side on which the word would appear. The encoding task was presented next, either “living or non-living?” (animacy judgment) or “mobile or immobile?” (mobility judgment, not shown). Finally, a word was presented directly above the encoding question; participants had 3500 ms to respond. Retrieval trials began with presentation of one of three cues (“Side”, “Question”, or “Odd/Even”). After a 1000 ms delay, a word was presented. On Side and Question trials, the word came from the immediately preceding encoding block, while on Odd/Even trials the word was a numeral (e.g., “seventy-seven”). Finally, a response screen was presented and persisted until the participant responded or 10 seconds had elapsed. The response options for a Side trial are displayed. On Question trials, “left” and “right” were replaced with “living/non-living” and “mobile/immobile”, respectively; on Odd/Even trials they were replaced with “odd” and “even”.

*Figure 2*. Encoding (A) response accuracy and (B) correct response time (RT). Responses were slower and less accurate in the mobility task versus the animacy task. There were no group differences, but data from controls and depressed participants are shown separately for comparison. Error bars = SEM.

*Figure 3*. Mean number of guesses by group, encoding task, and retrieval cue. Data are from 17 depressed and 11 healthy participants who guessed at least once in every condition. There was a main effect of *Task,* as all participants guessed less for words from the mobility (left panel) versus the animacy task (right panel). There was also a main effect of *Cue*, as participants guessed less for words shown under the Question cue (blue bars) versus the Side cue (green bars). Moreover,in the MDD group the effect of cues on guessing was pronounced for words from the mobility task. Error bars = SEM, \**p* = 0.007.

*Figure 4*. Source memory accuracy (A) under Question (blue bars) and Side (green bars) cues, and for (B) Question minus Side difference scores. In both panels, the left column shows data for words from the mobility task, and the right panel shows data for words from the animacy task. For the animacy task, both groups show lower accuracy under Question versus Side. By contrast, there was a *Group* x *Cue* interaction for words from the mobility task, because the MDD group shows better memory under the Question versus Side cue but the controls do not. Bar heights correspond to mean, error bars = SEM, \* *p* = 0.015.

*Figure 5.* (A) The percentage of high confidence responses as a function of group, cue, and task. All participants were more confident when responding to words from the mobility task (left panel) versus the animacy task (right panel) and when responding to the Question cue (blue bars) versus the Side cue (green bars). Depressed adults were less confident than controls in response to the Side cue but not the Question cue. Exploratory *t*-tests revealed thatdepressed adults were significantly more confident when responding to the Question versus Side cue for words from both encoding tasks. (B) Mean correct RT data; all participants responded more slowly to the Question cue (blue bars) versus the Side cue (green bars). Error bars = SEM, \**p*s < 0.001.

*Figure 6*. Mass univariate analysis of *Question* minus *Odd/Even* difference waves, from 400-800 ms (top), 800-1400 ms (middle), and 1400-2000 ms (bottom). The data are collapsed across groups as there were no significant between-group differences. On the topographies, electrodes in significant clusters are marked with white circles. The electrode that showed the strongest condition effect in each cluster per time window is marked in red, and waveforms from that electrode are plotted separately for each condition, with the time window shaded in gray. Electrode numbers (e.g., “e109”) give the position on the EGI cap—see the Supplement for a complete map.

*Figure 7*. Mass univariate analysis of *Side* minus *Odd/Even* difference waves, from 400-800 ms (top), 800-1400 ms (middle), and 1400-2000 ms (bottom). The data are collapsed across groups as there were no significant between-group differences. On the topographies, electrodes in significant clusters are marked with white circles. The electrode that showed the strongest condition effect in each cluster per time window is marked in red, and waveforms from that electrode are plotted separately for each condition, with the time window shaded in gray. Electrode numbers (e.g., “e83”) give the position on the EGI cap—see the Supplement for a complete map. No significant differences between the conditions were found from 400-800 ms.

*Figure 8*. Mass univariate analysis of *Question* minus *Side* difference waves, for words from the animacy task, from 400-800 ms (top), 800-1400 ms (middle), and 1400-2000 ms (bottom). The data are collapsed across groups as there were no significant between-group differences. On the topographies, electrodes in significant clusters are marked with white circles. The electrode that showed the strongest condition effect in each cluster per time window is marked in red, and waveforms from that electrode are plotted separately for each condition, with the time window shaded in gray. Electrode numbers (e.g., “e16”) give the position on the EGI cap—see the Supplement for a complete map. An orange line separates the two clusters identified from 800-1400 ms.

*Figure 9*. Group differences in the mass univariate analysis of *Question* minus *Side* difference waves, for words from the mobility task, from 400-800 ms (top) and 800-1400 ms (middle); bottom panel shows the data averaged over all significant electrodes in each cluster, in each time window. On the topographies, electrodes in significant clusters are marked with white circles. The electrode that showed the strongest condition effect in each cluster per time window is marked in red, and waveforms from that electrode are plotted separately for each condition, with the relevant time window shaded in gray. Electrode numbers (e.g., “e16”) give the position on the EGI cap. The data in each time window were characterized by *Group* x *Cue* interactions, as depressed participants generated a stronger response for Question versus Side hits while controls showed the opposite pattern.

*Figure 3*. Waveforms elicited by correct responses to the Question (black), Side (red), and Odd/Even (blue) cues. Representative electrodes from the left and right hemisphere are depicted for frontal and parietal scalp; the late posterior negativity (LPN) was maximal at the midline occipital electrode, Oz. Gray shading demarcates the parietal ERP associated with recollection, asterisks indicate reduced parietal activity in depressed adults.

*Figure 4*. Topographical maps of *t*-values for activity elicited by Question and Side hits, with activity on correct Odd/Even trials subtracted out (one-sample tests against zero). Columns correspond to the three time windows analyzed (400-800, 800-1400, 1400-2000 ms). Electrodes in clusters associated with significant within-group effects are shown in white. Between-group comparisons revealed no differences.

*Figure 5*. Topographical maps of *t*-values for Question minus Side difference waves, sorted by group and encoding task. Columns correspond to the three time windows analyzed (400-800, 800-1400, 1400-2000 ms). Electrodes in clusters associated with significant effects are shown in white. Paralleling the behavioral analyses, there were MDD > control differences in response to words from the mobility task but not the animacy task.

*Figure 6.* ERP amplitudes sensitive to recollection are related to sleep quality in depressed adults. There were significant negative correlations between sleep disturbance as measured by the PSQI (*x*-axis) and ERP amplitudes captured by the Question minus Side difference wave for words from the mobility task (*y­*-axis) in the 400-800 (left) and 800-1400 (right) ms time windows.