**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. Participants 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 recent symptoms of depression and anxiety, trait rumination, and sleep quality over the last month, respectively. 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*). 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), and then analyzed using *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 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 selected this response option more frequently 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.

**Group-level analyses**. We first inspected the ERP waveforms associated with correct responses to the Question, Side, and Odd/Even cues, regardless of encoding task. There was a clear group difference in the parietal ERP from 400-800 ms (see Results), thus we extracted mean amplitude data over this window from electrodes in the left (P1, P3, P5, P7) and right (P2, P4, P6, P8) hemispheres for a *Group* x *Cue* x *Hemisphere* ANOVA. This focus on a few electrodes in one time window constitutes the traditional approach to ERP analysis used in many studies of recollection (Hayama, Johnson, & Rugg, 2008; Rugg & Curran, 2007; Wilding & Rugg, 1996).

Two additional analyses used a newer approach and focused on difference waves. In the first 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). The second analysis was intended to parallel the memory accuracy data, which were characterized by a *Group* x *Cue* x *Encoding Task* interaction. To identify activity mediating this interaction, we computed “Question minus Side” difference waves separately for words from the mobility and animacy tasks 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. 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 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.

**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 plus more depression, anxiety, and rumination, 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**. Eleven controls and seventeen depressed participants guessed at least once in every cell of the design and were included in the *Group* x *Cue* x *Task* ANOVA; their data are shown in Figure 3. Because no participant guessed on an Odd/Even trial, this condition was omitted. Moreover, five participants (two controls, three depressed) did not guess at all and a further 15 participants (ten controls, five depressed) did not guess in at least one cell and so were excluded here. 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 2 suggested that, in the MDD group, the effect of cue type on guessing was pronounced for words from the mobility task. An exploratory *t*-test confirmed that depressed participants guessed less frequently for words from the mobility task presented under the Question cue versus the Side cue, *t*(16) = -3.11, *p* = 0.007, *d* = 0.51. By contrast, the effect of cue on guessing was not reliable for words from the animacy task considered alone, *t*(16) = -1.29, *p* = 0.22, and 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 guesses were less frequent in response to words from the mobility task versus the animacy task and in response to the Question cue versus the Side cue, and in the MDD group the combination of these two factors (i.e., words from the mobility task presented under the Question cue) led to especially few guesses relative to 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 source accuracy under the Question versus the Side cue), 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 for words from the mobility task, but accuracy did not vary by cue in the controls.

**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. We conducted exploratory *t*-tests on the percentage of high confidence responses under the Question versus Side cue for words from each encoding task in the MDD group, and confirmed that accuracy was significantly higher under the Question versus Side cue for 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, when each were considered alone. Thus, the effect of cue type on confidence did not vary by encoding task in the MDD group. This contrasts with the results obtained for source accuracy and number of guesses, where the difference between responses to the Question versus Side cue was magnified for words from the mobility task in the MDD group.

**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 vs. 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 summary**. At encoding, mobility judgments were made more slowly and less accurately than animacy judgments, and this appears to have supported better retrieval as particpants in 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 in response to 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 depressed group. Depressed participants guessed least frequently to words from the mobility task presented under the Question cue, 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, whereas there was no effect of cue type on accuracy in the control group. This pattern differed noticeably from what was observed with words from the animacy task, where both groups were less accurate in response to the Question cue versus the Side cue. In short, the mobility task and Question cue reduced guessing and supported confident responding in all participants, and the combination of these two factors led to an accuracy boost in the MDD group. **STOPPED**

**ERPs**

Figure 3 displays waveforms elicited by correct responses to Question, Side, and Odd/Even cues. There was robust activity over parietal electrodes from 400-800 ms in controls that was decreased in MDD, yielding an effect of *Group*, *F*(1,46) = 4.35, *p* = 0.043, *d* = 0.40. There was also an effect of *Cue*, *F*(2,92) = 10.37, *p* < 0.001, with reliable differences between all conditions (REGWQ; Question > Side > Odd/Even, *ps* < 0.043). These data suggest that recollection was strongest under the Question cue and reduced in MDD. In both groups, the LPN is apparent at Oz from 800-2000 ms on Question and Side (but not Odd/Even) trials, and it extends over left frontal cortex on Question trials.

PLEASE INSERT FIGURE 3 ABOUT HERE

To test our *a priori* hypothesis, we subtracted activity on Odd/Even trials from Question and Side trials. Figure 4 shows that the Question condition drove activity over left parietal electrodes from 400-800 ms, although this effect was only reliable in controls (a negative difference over right frontal cortex was only reliable in the MDD group). From 1400-2000 ms, this subtraction revealed a negative difference over left PFC in both groups. By contrast, the Side condition elicited an LPN over midline posterior sites from 800-1400 ms. These patterns replicate prior results (Bergström et al., 2013), but between-groups tests yielded no reliable findings.

PLEASE INSERT FIGURE 4 ABOUT HERE

***Group x Cue x Encoding Task***. Our planned ERP analysis did not reveal group differences, but it was not designed to capture the *Group* x *Cue* x *Encoding Task* interaction that characterized source accuracy. To address this limitation, we computed Question minus Side difference waves for words from each encoding task and submitted them to within and between-groups analysis, duplicating our approach to the accuracy data. Figure 5 shows that, in depressed adults, the Question minus Side difference varied drastically by encoding task (see Table 2). Words from the mobility task elicited sustained activation over left parietal cortex, leading to significant effects in all time windows. By contrast, words from the animacy task elicited a negativity over fronto-central sites that was stronger over the left hemisphere; again, significant differences were observed in all time windows. In controls, no significant effects were seen in any time window. Between-groups comparisons revealed reliable differences for the mobility task over left centro-parietal electrodes from 400-800 and 800-1400 ms, with stronger activation in the MDD group. Thus, the Question (minus Side) cue had a strong, task-dependent effect on brain activity in MDD that was muted in controls, paralleling the source accuracy data.

PLEASE INSERT FIGURE 5 AND TABLE 2 ABOUT HERE

**Individual Differences**

We computed Pearson correlations in the MDD group to determine if variation in depressive severity (BDI-II total), brooding rumination (RRS-Brooding), or sleep disruption (PSQI total) affected source accuracy or ERP amplitudes. We found no relationship with source accuracy, left parietal activity on Question trials averaged over encoding tasks, or left frontal activity on Question/animacy trials (|*r*s| < 0.31, *p*s > 0.15). However, as shown in Figure 6, parietal activity isolated by the Question minus Side subtraction for words from the mobility task was negatively correlated with PSQI scores from 400-800 ms and 800-1400 ms (*r*s < -0.47, *ps* < 0.02). To confirm that these results 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, ERP amplitude was lowest in those depressed adults who reported chronic sleep disruption, and this effect was not driven by depressive severity.

PLEASE INSERT FIGURE 6 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. All participants guessed less for words from the mobility versus the animacy task, and for words shown under the Question cue versus the Side cue. In the MDD group, the Question versus Side comparison was significant 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. The cue effect is similar across groups for the animacy task (lower accuracy under Question versus Side), but only the MDD group shows better memory under the Question versus Side cue for words from the mobility task. 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 versus the animacy task and when responding to the Question cue versus the Side cue; depressed adults were less confident than controls in response to the Side cue but not the Question cue. Exploratory *t*-tests confirmed thatdepressed adults were significantly more confident when responding to the Question versus Side cue for words from either the mobility or animacy tasks. (B) Mean correct RT data; all participants responded more slowly to the Question cue versus the Side cue. Error bars = SEM, \**p*s < 0.001.

*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.