Biological Psychiatry: CNNI

Archival Report

Reduced Theta Power During Memory Retrieval in Depressed Adults

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ABSTRACT

BACKGROUND: Major depressive disorder (MDD) is associated with poor recollection, but the neural mechanisms responsible for this deficit are unclear. Recollection is supported by interactions between the hippocampus and cortex that appear to be mediated by oscillatory activity in the theta band (4-7 Hz) and that are elicited during source memory retrieval. Therefore, we tested the hypothesis that evoked theta power during source memory retrieval would be reduced in MDD, as this would provide a physiological basis for deficient recollection in adults with depression.

METHODS: Morlet wavelets were applied to event-related potentials collected from 24 unmedicated adults with MDD and 24 healthy control adults during the retrieval of source and semantic memories. Whole-scalp analyses focused on group differences in evoked theta power.

RESULTS: There were no group differences in behavior. Nevertheless, from 400 to 799 ms, theta power was broadly reduced in adults with depression versus healthy adults. This reduction was observed during source and semantic retrieval. Parietal midline electrodes showed significantly reduced theta power during source—but not semantic—retrieval in adults with depression versus healthy adults in this interval. Furthermore, theta power over parietal midline sites from 400 to 799 ms was more strongly related to source memory accuracy in healthy adults versus adults with depression.

CONCLUSIONS: Relative to healthy control adults, adults with depression showed reduced theta power during memory retrieval and a weaker relationship between parietal midline theta power and source memory accuracy. These findings indicate that abnormal theta signals may contribute to memory deficits in adults with MDD.

Keywords: Depression, EEG, Memory, Retrieval, Theta, Time frequency

https://doi.org/10.1016/j.bpsc.2019.03.004

Behavioral research has revealed poor recollection in adults with depression (1–5). Recollection refers to the retrieval of spatiotemporal details that define an encoding episode (6,7), and it depends on corticohippocampal interactions (8–11). The memory deficits seen in depression may reflect disrupted communication between the hippocampus and cortex (12), such that adults with depression cannot retrieve information as effectively as healthy control adults can. We investigated this issue by applying time-frequency analysis to event-related potentials (ERPs) collected from adults with major depressive disorder (MDD) and healthy control adults during retrieval; the ERPs and extensive behavioral analyses have been described previously (13).

We focused on evoked theta (4-7 Hz) power (14) for three reasons. First, hippocampal theta signals are robust in humans (15) and nonhuman animals (16). Because the hippocampus is critical for encoding and retrieval, this suggests that memory-related signals may be carried at the theta frequency. Second, there is cross-species evidence that communication between the hippocampus and cortex, and between different cortical sectors, involves theta synchrony (17,18). This may be important because successful retrieval involves the coordinated recovery of information from diverse cortical and subcortical territories. Third, human electroencephalogram (EEG) studies have linked increased theta power to successful retrieval (19–21). This relationship appears particularly strong when recollection is elicited, such as when participants must specify the source of an item (the context in which it was studied) rather than simply indicating that it was previously encountered (22). Tying these strands together, we reasoned that impaired recollection in MDD could reflect disrupted theta signals during retrieval.

To test this hypothesis, we reanalyzed the ERP data from our recent study of source memory (13). During encoding, the participants viewed neutral words shown on the left or right side of a monitor (perceptual source) in the context of animacy or mobility judgments (conceptual source). At retrieval, the words were shown again under cues prompting perceptual retrieval (Side cue; "Was this word shown on the left or right?") or conceptual retrieval (Question cue: "What judgment did you make for this word?"). On Number trials, a numeral word (e.g., ninety-six) was shown and the participant indicated whether it was odd or even. Number trials controlled for the sensorimotor demands present on Question and Side trials, but because

 ISSN: 2451-9022

they required participants to draw on general knowledge rather than their memory for a recent event, the Number trials were intended to elicit retrieval from semantic rather than episodic memory. By contrasting Question and Side trials with Number trials, we hoped to detect brain activity associated with episodic memory. We assumed that such activity would primarily reflect recollection because of the need to retrieve encoding details. However, participants sometimes make accurate source judgments even when recollection fails (23); thus, we could not rule out the possibility that such contrasts might also reveal activity associated with familiarity.

Replicating prior studies (24–27), successful source retrieval was associated with positive ERPs over left parietal scalp from 400 to 800 ms, as well as a long-lasting negative deflection from 800 to 2000 ms called the late posterior negativity. The late posterior negativity was centered over posterior midline electrodes and extended over left frontal scalp during retrieval of conceptual source memories (13). Surprisingly, however, these contrasts did not reveal group differences, which only emerged when we considered interactions between encoding and retrieval. Briefly, the combination of deep encoding plus conceptual source retrieval enhanced memory accuracy and boosted the amplitude of left centroparietal ERPs in adults with depression more than in control adults (13). These results are consistent with Hertel's cognitive initiative framework (28), and the ERPs provided insight into underlying cognitive operations. Nevertheless, the results were complex, and the failure to find stronger group differences was surprising.

We undertook the current analysis to see whether time-frequency decomposition would yield additional information. In particular, ERP analyses yield no data about spectral power, and thus a negative effect of MDD on theta signals could be overlooked. To circumvent this problem, we applied Morlet wavelets to the ERPs to assess evoked theta power. We made three predictions. First, we expected reduced theta power in depressed versus healthy participants during source retrieval. Second, given limited evidence for disrupted semantic memory in depression, we did not anticipate group differences on Number trials. Third, within each group we expected higher theta power during source versus semantic retrieval, because only source retrieval should involve recollection (20).

METHODS AND MATERIALS

Participants and Self-report

The data were obtained from 24 unmedicated adults who met criteria for current MDD based on the Mini-International Neuropsychiatric Interview (29) and 24 control adults with no current or past Axis I disorder psychopathology. In the MDD group, no current or past history of any other DSM-IV Axis I disorder diagnosis was allowed with the exception of generalized anxiety, social anxiety, and specific phobias because these are often comorbid with MDD. Participants were right-handed, reported no current or past neurological conditions, and consented to a protocol approved by the Partners HealthCare Human Research Committee. The groups did not differ on gender (MDD: 15 female adults, 9 male adults; control: 13 female adults, 11 male adults; $\chi^2 < 1$), age (mean ± SD, MDD: 29.79 ± 10.85; control: 30.58 ± 11.32; $t < 1$), or years of education (MDD: 16.29 ± 2.49; control: 16.92 ± 2.20; $t < 1$), all $ps > .34$. Immediately after the EEG session, participants completed the Beck Depression Inventory-II (30), the Mood and Anxiety Symptom Questionnaire (31), the Ruminative Responses Scale (32), and the Pittsburgh Sleep Quality Index (33). The Wechsler Test of Adult Reading (WTAR) (34) was used to estimate IQ. One control adult did not complete the Mood and Anxiety Symptom Questionnaire, one participant with depression did not complete the Pittsburgh Sleep Quality Index, and WTAR data from non-native English speakers (2 control adults, 2 MDD adults) were not analyzed, as WTAR results may be invalid in such cases.

The results from these measures are shown in Table 1. Based on Beck Depression Inventory-II scores, the adults with depression were experiencing moderately severe depressive symptoms. Relative to control adults, they reported more anxiety, more rumination, and poorer sleep over the last month. There was no group difference in IQ as estimated by WTAR scores. Two adults with depression met criteria for generalized anxiety disorder in the past 6 months, seven reported one or more lifetime panic attacks, and a small number reported subthreshold symptoms of anxiety disorders (social anxiety, $n = 2$; agoraphobia, $n = 2$; panic attacks, $n = 2$).

Task and Stimuli

The task was programmed in PsychoPy (http://www.psychopy.org) (35) and consisted of six encoding-retrieval cycles. Each encoding run involved displaying 16 neutral words on the left or right of fixation for 3500 ms. Words were presented above a question: "Living or nonliving?" (an animacy task) or "Mobile or immobile?" (a mobility task). Participants responded by pressing a button (c or m) on a keyboard; a jittered interval (500–2000 ms) separated the trials. After encoding, a three-digit number (e.g., 557) was shown, and the participant counted down in steps of three for 30 seconds to

Table 1. Self-Report Data

Variable	Control Adults ($n = 24$)	Adults With Depression ($n = 24$)	p
BDI-II	1.29 (2.22)	25.38 (8.69)	<.001
MASQ-GDA	13.04 (2.10)	21.38 (7.04)	<.001
MASQ-AA	17.65 (0.98)	24.00 (8.24)	.001
MASQ-GDD	13.65 (2.08)	38.46 (10.0)	<.001
MASQ-AD	45.61 (12.29)	86.54 (8.74)	<.001
RRS-Dep	17.96 (4.73)	32.96 (4.51)	<.001
RRS-Brood	7.75 (2.38)	12.54 (2.99)	<.001
RRS-Reflect	9.04 (3.80)	12.25 (2.97)	.002
PSQI[a]	3.00 (2.00)	8.48 (2.73)	<.001
WTAR	116.73 (11.58)	117.09 (7.84)	.90

Data are presented as mean (SD). Statistics reflect between-group t tests.

AA, Anxious Arousal; AD, Anhedonic Depression; BDI-II, Beck Depression Inventory-II; Brood, brooding subscale; Dep, depression subscale; GDA, General Distress: Anxious symptoms; GDD, General Distress: Depressive symptoms; MASQ, Mood and Anxiety Symptoms Questionnaire; PSQI, Pittsburgh Sleep Quality Index; Reflect, reflection subscale; RRS, Ruminative Response Scale; WTAR, Wechsler Test of Adult Reading.

[a]PSQI scores ≤ 5 indicate good sleep quality, and scores > 5 indicate poor sleep quality.

clear working memory (36). No EEG data were collected in these task phases.

Each retrieval run included 48 trials consisting of a cue (1000 ms), a word (3000 ms), and a response screen (up to 10,000 ms). The cue was Question, Side, or Odd/Even. On Question and Side trials, the words were drawn from the most recent encoding list and the task was to indicate whether each word had been shown with the animacy or mobility task (Question cue) or on the left versus right (Side cue). On Number trials (Odd/Even cue), the words were numerals (e.g., ninety-six) and the participant had to indicate whether each one was odd or even. The EEG analysis focused on neural activity when the words were onscreen as this was when retrieval should have occurred.

To avoid overlap between EEG signals elicited by memory versus motor activity, participants could not respond until the response screen appeared, 3000 ms after words were shown. The response screen listed the options for each cue (Question: living/nonliving vs. mobile/immobile; Side: left vs. right; Number: odd vs. even) with two levels of confidence (high/low) for each option. Following prior studies (37), a "guess" option was provided should participants be unable to recover information favoring either source. Participants responded by pressing the c and v keys with the first two fingers of their left hands and the b, n, and m keys with the first three fingers of their right hands. The options remained onscreen until the participant pressed a button or 10 seconds elapsed. A jittered interval (500–2000 ms) separated the trials. Trial order was randomized and a fixation cross was presented throughout.

The stimuli were 100 neutral words from the Medical Research Council Psycholinguistic Database (38), 25 from each of four categories: "living/immobile" (e.g., elm), "nonliving/immobile" (e.g., hill), "living/mobile" (e.g., fox), and "nonliving/mobile" (e.g., car) [see (13) for a complete list]. Neutral words were used to identify effects of MDD on memory that do not depend on mood congruency. Four words were used in practice trials, with the rest shown in the experiment.

Behavioral Analysis

As described previously (13), encoding accuracy was high (≥92% correct) for both groups. For simplicity and to reduce overlap with our prior publication (13), we do not consider the encoding data further. We cleaned the retrieval data by dropping trials with no response or where the natural logarithm of response time (RT) exceeded the participant's mean ± 3 SD (<1% of retrieval trials). Next, we excluded guess responses (<7% of trials) before computing group × cue (Question, Side, Number) analyses of variance on accuracy (percentage correct), confidence, and correct RT. For RT, analyses of variance were computed on log-transformed data, but results are described using untransformed RT data for interpretability. Analyses of variance were implemented in the R software (39) library afex (40). Post-hoc Tukey tests were computed with the lsmeans package (41). α was set to .05. All tests were two-tailed unless stated otherwise.

EEG Recording and Analysis

Recording. The EEG was recorded with a 128-sensor HydroCel GSN (Electrical Geodesics Inc., Eugene, OR) 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).

Preprocessing. EEG preprocessing was conducted with the EEGLAB (42) and ERPLAB (43) toolboxes for MATLAB (The MathWorks, Inc., Natick, MA). EEG data were merged, rereferenced to the average of all electrodes, and filtered (0.1–30 Hz). Bad channels were interpolated; independent component analysis was used to remove activity reflecting blinks, horizontal electrooculogram, and electrocardiogram; and the cleaned data were time locked to word onsets and segmented (−200 to 2000 ms). The prestimulus 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. Data from guess trials were excluded and there were too few clean segments to analyze misses, so we focused on correct responses (24,44–46). There were no group differences in the number of clean segments available (Question: MDD, 49.5 ± 11.6; control, 47.63 ± 13; Side: MDD, 48.21 ± 11.5; control, 48.86 ± 14.02; Number: MDD, 73.79 ± 10.43; control, 69.54 ± 11.42; $ps > .18$). Finally, segments were averaged to form ERPs.

Time-Frequency Analysis. Spectral decomposition of ERPs was achieved by convolution with complex Morlet wavelets (*CMW* in the following equation) (47), which were structured as follows:

$$CMW = A * \exp[-t^2/(2 * s^2)] * \exp(2 * pi * f * i)$$

Here, t is time, f is frequency, and i is the square root of -1. $s = n/(2*pi*f)$, where n is the number of cycles in the wavelet. We used $n = 3$ to increase our ability to detect transient activity (47). We set $A = 1/[\text{sqrt}(s)*pi^{(1/4)}*2]$.

The theta band was divided into four frequencies (4, 5, 6, and 7 Hz). For each center frequency, the complex Morlet wavelet was convolved with each participant's ERPs. The absolute value of the resulting signal was squared to give the instantaneous power, and results from all frequencies in the theta band were then averaged to give evoked theta power (14).

We took two steps to avoid edge effects. First, we applied a Hanning taper to rapidly dampen the first and last 2.5% of the ERPs. Second, we analyzed data from 0 to 1600 ms poststimulus, as edge effects should be minimal in this window (given the 200-ms prestimulus baseline and the fact that epochs ended at 2000 ms). The 400- to 800-ms period is when ERP effects related to recollection are commonly detected (27), and the late posterior negativity typically emerges at about 800 ms (48). Thus, this analysis window should capture neural signals related to source memory.

Statistical Analysis. The primary analysis consisted of between-groups Student's t tests on evoked theta power at every electrode on Question, Side, and Number trials. To estimate the false-positive rate, we ran 10,000 simulations in which we generated two 24 × 128 matrices of random values, computed 128 between-group Student's t tests (comparing 24 vs. 24 values at each "electrode"), and then we identified

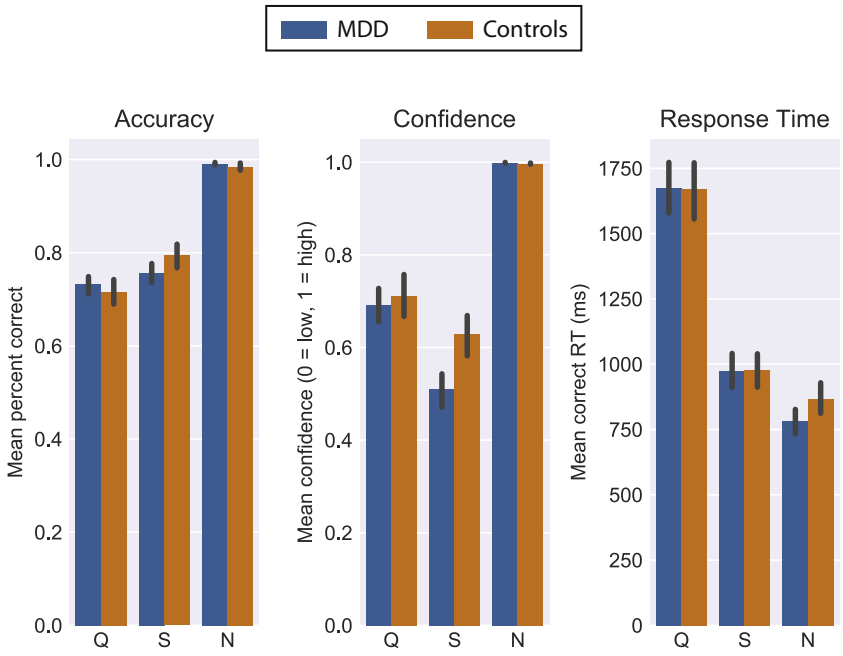

Figure 1. Retrieval accuracy plus confidence and response time (RT) on correct trials. Analysis of these data did not reveal group differences, but results are shown separately for adults with depression and healthy adults to permit visual comparison. Error bars show SEM. MDD, major depressive disorder; N, Number; Q, Question; S, Side.

the largest cluster of contiguous significant ($p < .05$) electrodes. We saved the largest cluster from each simulation to create a distribution of maximal cluster sizes. The 95th percentile corresponded to a three-electrode cluster, so only clusters at least this large were considered significant. In exploratory analyses, we used the same approach to examine between-group differences in evoked delta (0.5–2.5 Hz), alpha (8–12 Hz), and beta (13–31 Hz) power. We do not report on gamma power because the ERPs were low-pass filtered at 30 Hz.

In a secondary analysis we computed within-group Student's *t* tests on theta power for Question versus Number and Side versus Number contrasts. These were expected to reveal increased theta power for source versus semantic retrieval (20). To explore brain-behavior relationships, we computed correlations between Question, Number, and Source accuracy and theta power at every electrode. To estimate the false-positive rate for this analysis, we conducted another simulation in which we correlated the control adults' Question accuracy data with a 24 × 128 matrix of random values, repeated this process 10,000 times, and each time identified the largest cluster of contiguous electrodes that showed a significant ($p < .05$) correlation. This simulation indicated that a five-electrode extent would be expected by chance 5% of the time; thus a five-electrode cluster threshold was set for our correlational analysis.

RESULTS

Behavior

The retrieval accuracy, confidence, and RT data are shown in Figure 1 (for mean ± SD values, see Supplemental Table S1). Analysis of these data revealed only main effects of Cue, Fs > 114, ps < .001, η_p^2 values > .7; neither the group effect nor the group × cue interaction was significant in any analysis, ps > .08. On Number trials, participants were highly accurate, were confident, and responded quickly. Question and Side trials were characterized by lower accuracy and confidence and slower RTs. Responses on Question trials were less accurate and slower than on Side trials, but they were more confidently made. All pairwise comparisons were significant for accuracy, confidence, and RT (ps < .001).

Group Differences in Theta Power

Figure 2 depicts electrodes that showed significantly stronger theta power in healthy adults versus adults with depression for Question (top), Side (middle), and Number (bottom) hits. No electrodes showed greater theta power in adults with depression. Electrodes shown in gray are not in a cluster of at least three electrodes and may be false positives. By contrast, electrodes shown in blue, green, and red formed distinct clusters whose size exceeded the correction for multiple comparisons.

Two results are noteworthy. First, the control > MDD difference was evident for source retrieval (Question, Side conditions) but also extended to semantic retrieval (Number condition). Second, the effect of MDD was clearest in the 400- to 799-ms window. Specifically, although a group difference was evident in every interval for at least one condition, the 400- to 799-ms interval was the only one in which the group difference was present in every condition.

Exploratory analysis revealed control > MDD differences—but never the opposite—in the delta (Supplemental Figure S1), alpha (Supplemental Figure S2), and beta (Supplemental Figure S3) bands. The group differences in these bands were qualitatively weaker than in the theta band, however, especially on Side and Number trials.

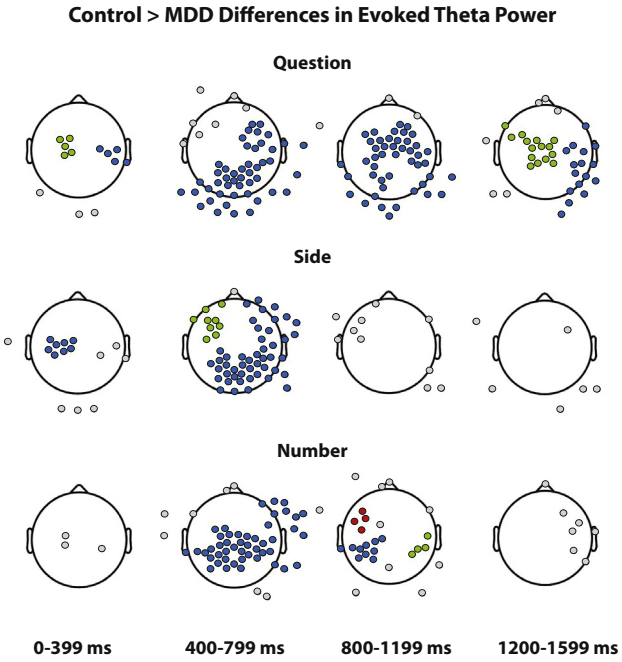

Figure 2. Electrodes showing a significant ($p < .05$) control > major depressive disorder (MDD) difference in evoked theta power on Question (top), Side (middle), and Number (bottom) trials. Electrodes shown in gray are not part of a cluster of at least three electrodes and so may be false positives. Electrodes shown in the other colors (blue, green, or red) are part of distinct clusters that are sufficiently large to survive correction for multiple comparisons. No electrodes showed a significant MDD > control difference.

Condition Effects on Theta Power

In both groups, theta power was greater on Question versus Number trials (control group, see Supplemental Figure S4; MDD group, see Supplemental Figure S5) and on Side versus Number trials (control group, see Supplemental Figure S6; MDD group, see Supplemental Figure S7). These condition effects were broadly distributed and at least one significant cluster appeared in each interval, except for the 0- to 399-ms interval for the Question versus Number contrast in control adults.

Brain-Behavior Correlations

Figure 3A shows that in control adults, source memory accuracy was positively correlated with theta power at 17 electrodes during the 400- to 799-ms interval. Side accuracy was correlated with two electrodes over left frontal scalp, and Question accuracy was correlated with two electrodes over right central scalp; these clusters did not meet the five-electrode threshold. By contrast, 13 electrodes were bunched over the parietal midline. In this region, clusters of 10 and eight electrodes showed correlations with accuracy in the Question (Figure 3; red) and Side (Figure 3; blue) conditions, respectively; five electrodes showed correlations with both conditions (Figure 3; purple). Of the 13 electrodes, six showed a significantly stronger correlation in healthy adults versus adults with depression (Figure 3; larger circles). Moreover, as shown in Figure 3B, this cluster was characterized by a group × cue interaction, $F_{1.81,83.38} = 5.37$, $p = .008$, $\eta_p^2 = .10$, driven by group differences on Question ($p < .03$) and Side ($p < .001$) trials, but not on Number ($p = .79$) trials, from 400 to 799 ms. No significant clusters emerged in the other intervals in control adults or in any interval in the MDD group. Number accuracy was not significantly correlated with any electrode clusters in either group in any interval.

Figure 3C shows correlations averaged over all 13 electrodes. Theta power was positively related to accuracy in healthy adults but not in adults with depression on Question (control adults: $r = .52$, $p = .01$; adults with MDD: $r = -.11$, $p = .62$) and Side (control adults: $r = .48$, $p = .02$; adults with MDD: $r = .00$, $p = 1.0$) trials. These correlations differed significantly by one-tailed Z test (Question: $Z = 2.24$, $p = .013$; Side: $Z = 1.67$, $p = .047$). As an alternative approach to these data, we regressed average theta power at the 13 posterior midline electrodes on condition (Question, Side), group, and accuracy. This returned an effect of accuracy ($\beta = 0.54$, $p < .001$) and a group × accuracy interaction ($\beta = -0.04$, $p = .024$), because accuracy on Question and Side trials was positively related to theta power in healthy adults but not adults with depression.

DISCUSSION

This analysis yielded four findings. First, evoked theta power was broadly reduced in adults with depression versus healthy adults during retrieval of source but also semantic memories, with this effect being strongest from 400 to 799 ms post-stimulus. Second, in both groups, theta power was higher during source versus semantic retrieval. Third, theta power over the parietal midline was higher during source retrieval—but not semantic retrieval—in healthy adults versus adults with depression from 400 to 799 ms. Fourth, source accuracy was positively correlated with parietal midline theta power from 400 to 799 ms in control adults but not in adults with depression. Overall, these data point to disrupted theta signals as a possible mechanism underlying deficient recollection in MDD.

It is unclear why depression was associated with reduced theta power, but disrupted sleep may play a role. In nonhuman animals, sleep deprivation decreases the excitability of hippocampal neurons (49), disrupts long-term potentiation (50), and reduces the generation of the hippocampal theta rhythm (51). In this study, adults with depression reported poorer sleep over the past month than did the control adults. Thus, we speculate that sleep deprivation may have contributed to reduced theta power in MDD.

Midline parietal electrodes were characterized by group differences in theta power on Question and Side (but not Number) trials, and in the strength of correlations between theta power and source memory accuracy. These results are consistent with the fact that the parietal memory network (PMN) (52) makes critical contributions to episodic retrieval (24,53–56). For example, intervention studies have established a causal role for the PMN in retrieval success, which appears to reflect its connectivity with the hippocampus. When the PMN is stimulated, functional connectivity with the hippocampus increases and recollection precision improves (57,58). By contrast, inhibition of the PMN, especially the precuneus, impairs memory performance (59,60). We cannot be certain of the generators of our scalp-recorded effects. Nonetheless, a prior study used a similar paradigm in conjunction with

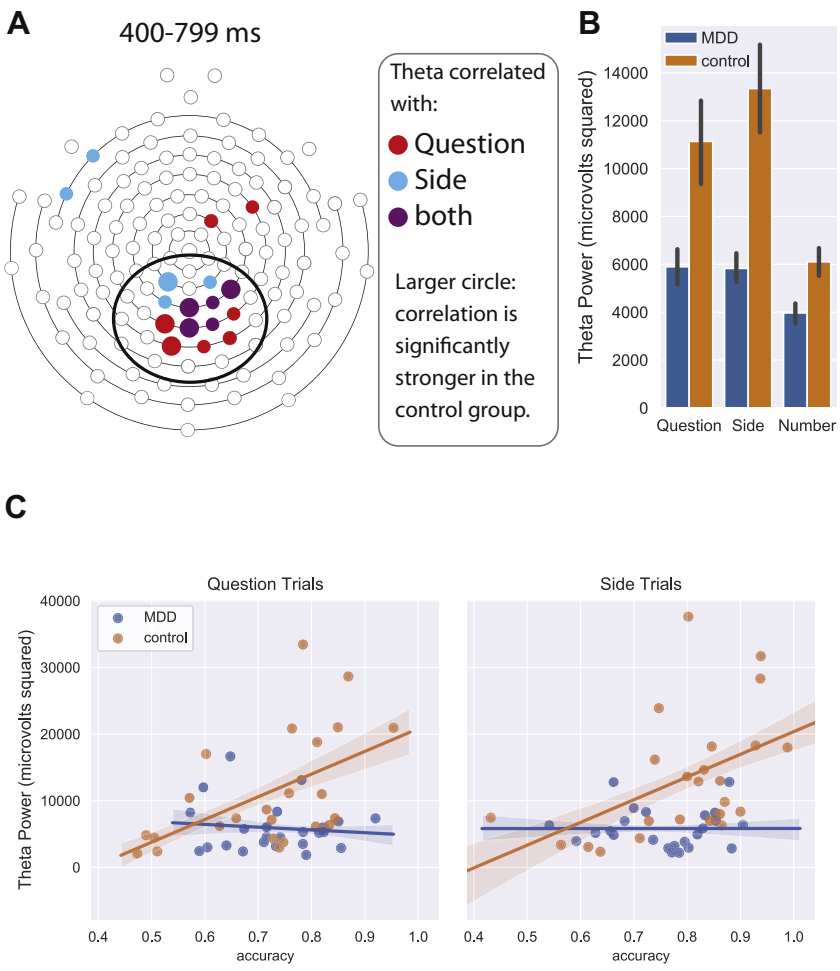

Figure 3. **(A)** Topography shows electrodes in which evoked theta power was positively correlated with accuracy on Question (red) trials, Side (blue) trials, or both (purple) in the healthy control group; no positive correlations were seen in the major depressive disorder (MDD) group. Enlarged electrodes indicate sites at which the strength of the theta-accuracy correlation differed significantly between groups by Fisher's *Z* test (*p*s $< .05$). **(B)** At the 13 electrodes over the parietal midline (circled in **A**), theta power was significantly higher in control adults versus adults with depression on Question and Side trials, but not Number trials (group × cue interaction, $p = .008$). **(C)** In control adults, average theta power over the 13 parietal midline electrodes (circled in panel **A**) was significantly positively correlated with accuracy on Question (left) and Side (right) trials. No such correlations were observed in the MDD group.

functional magnetic resonance imaging and magnetoencephalography to show that successful source retrieval strongly recruited the PMN, especially the precuneus (24). In short, one would expect memory-related abnormalities in theta to be evident over parietal midline electrodes, as was observed in the MDD group; this may reflect dysfunction of the PMN.

This interpretation raises questions. For instance, if MDD affects episodic but not semantic memory, why was a group difference in theta power observed on Number trials? This result was unexpected and so our interpretation is speculative, but two considerations are important. First, our characterization of the Number trials may be flawed. We conceptualized the Number condition as requiring semantic retrieval because judging whether numerals are odd or even depends on general knowledge rather than memory for a specific event. However, the Number trials involved numerical cognition, and that is atypical of semantic memory tasks. Numerical cognition depends on parietal cortex (61) and can induce frontoparietal theta synchrony (62). Consequently, the group difference may have extended to Number trials because these trials drove a stronger theta response than a more standard semantic memory task would have. Second, MDD may involve a traitlike reduction in theta power that can be observed even when evoked theta signals are relatively weak. Indeed, empirical studies (63) and a recent review (64) emphasize that resting-state EEG data show reduced parietooccipital theta power in adults with depression versus healthy adults. Therefore, it may be possible to detect reduced parietooccipital theta power in adults with depression even if evoked theta power is weak (e.g., during semantic retrieval).

A second question is, If theta is important for memory, and if theta power was reduced in MDD, then why were there no group differences in behavior? The answer to this question is unknown. Other researchers have suggested that increased functional connectivity may help compensate for reduced EEG power in MDD (65), but whether such an account applies in this case is unclear. Thus, better characterizing the relationships between behavioral and EEG markers of memory retrieval in MDD remains an important goal.

Finally, it is interesting that the strongest effects consistently emerged from 400 to 799 ms. This is in line with prior ERP research (27) and with an intracranial study that found greater high gamma power for hits versus correct rejections in the left intraparietal sulcus from 300 to 700 ms (66). Intracranial

recordings from hippocampus indicate that signals distinguishing old versus new items emerge at 250 ms poststimulus (67). The PMN may accumulate such memory signals, sent from the hippocampus, to make memory-based decisions. Therefore, it may be that the temporal difference in the onset of memory signals across these two regions (~250 ms for hippocampus vs. ~300–400 ms for parietal cortex) reflects conduction delay between them (66).

It is important to acknowledge limitations. First, the design did not include new items. Therefore, while we assume that our paradigm elicited recollection because of the need to retrieve encoding details, we cannot rule out the possibility that familiarity may have contributed to our results. Second, low trial counts precluded examination of misses and comparisons of retrieval success versus failure. Third, the lack of group differences in behavior was unexpected. In our prior report, we found relatively subtle effects of MDD by examining the retrieval of words from each encoding task separately (13). Using emotional stimuli to drive stronger group differences in behavior that can then be related to EEG dynamics is a priority.

In conclusion, theta power was reduced in adults with depression during retrieval of source as well as semantic memories. This effect may reflect PMN dysfunction. Given the centrality of memory to cognitive function and the enormous burden placed on society by depression, we propose that future studies continue testing the hypothesis that abnormal theta signaling contributes to memory deficits in MDD.

ACKNOWLEDGMENTS AND DISCLOSURES

The research in this article was supported by the National Institute of Mental Health (Grant No. R00 MH094438-03 [to DD]) and the National Institute of General Medical Sciences (Grant No. 1P20GM109089-01A1 [to JFC]). Data collection was supported 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 thank Elyssa Barrick for recruiting the participants, collecting the data, and preprocessing the electroencephalogram recordings; and Victoria Lawlor for assistance with recruitment and testing.

In the last 3 years, DGD has received consulting fees from Pfizer, Inc., for work unrelated to this project. The other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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Received Nov 16, 2018; revised Feb 15, 2019; accepted Mar 11, 2019.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2019.03.004.

REFERENCES

1. Burt DB, Zembar MJ, Niederehe G (1995): Depression and memory impairment: A meta-analysis of the association, its pattern, and specificity. Psychol Bull 117:285–305.
2. Hertel PT, Milan S (1994): Depressive deficits in recognition: Dissociation of recollection and familiarity. J Abnorm Psychol 103:736–742.
3. Ramponi C, Barnard P, Nimmo-Smith I (2004): Recollection deficits in dysphoric mood: An effect of schematic models and executive mode? Memory 12:655–670.
4. MacQueen GM, Galway TM, Hay J, Young LT, Joffe RT (2002): Recollection memory deficits in patients with major depressive disorder predicted by past depressions but not current mood state or treatment status. Psychol Med 32:251–258.
5. MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT, *et al.* (2003): Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci U S A 100:1387–1392.
6. Yonelinas AP (2002): The nature of recollection and familiarity: A review of 30 years of research. J Mem Lang 46:441–517.
7. Yonelinas AP (2001): Components of episodic memory: The contribution of recollection and familiarity. Philos Trans R Soc B Biol Sci 356:1363–1374.
8. Eichenbaum H, Yonelinas AP, Ranganath C (2007): The medial temporal lobe and recognition memory. Annu Rev Neurosci 30:123–152.
9. Yonelinas AP, Aly M, Wang WC, Koen JD (2010): Recollection and familiarity: Examining controversial assumptions and new directions. Hippocampus 10:1178–1194.
10. Merkow MB, Burke JF, Kahana MJ (2015): The human hippocampus contributes to both the recollection and familiarity components of recognition memory. Proc Natl Acad Sci U S A 112:14378–14383.
11. Kirwan CB, Wixted JT, Squire LR (2010): A demonstration that the hippocampus supports both recollection and familiarity. Proc Natl Acad Sci U S A 107:344–348.
12. MacQueen G, Frodl T (2011): The hippocampus in major depression: Evidence for the convergence of the bench and bedside in psychiatric research? Mol Psychiatry 16:252–264.
13. Barrick EM, Dillon DG (2018): An ERP study of multidimensional source retrieval in depression. Biol Psychol 132:176–191.
14. Roach BJ, Mathalon DH (2008): Event-related EEG time-frequency analysis: An overview of measures and an analysis of early gamma band phase locking in schizophrenia. Schizophr Bull 34:907–926.
15. Lega BC, Jacobs J, Kahana M (2012): Human hippocampal theta oscillations and the formation of episodic memories. Hippocampus 22:748–761.
16. Buzsáki G (2002): Theta oscillations in the hippocampus. Neuron 33:325–340.
17. Lisman JE, Jensen O (2013): The theta-gamma neural code. Neuron 77:1002–1016.
18. Solomon EA, Kragel JE, Sperling MR, Sharan A, Worrell G, Kucewicz M, *et al.* (2017): Widespread theta synchrony and high-frequency desynchronization underlies enhanced cognition. Nat Commun 8:1704.
19. Hsieh LT, Ranganath C (2014): Frontal midline theta oscillations during working memory maintenance and episodic encoding and retrieval. Neuroimage 85:721–729.
20. Klimesch W, Schimke H, Schwaiger J (1994): Episodic and semantic memory: An analysis in the EEG theta and alpha band. Electroencephalogr Clin Neurophysiol 91:428–441.
21. Klimesch W, Doppelmayr M, Stadler W, Pöllhuber D, Sauseng P, Roehm D (2001): Episodic retrieval is reflected by a process specific increase in human electroencephalographic theta activity. Neurosci Lett 302:49–52.
22. Gruber T, Tsivilis D, Giabbiconi CM, Müller MM (2008): Induced electroencephalogram oscillations during source memory: Familiarity is reflected in the gamma band, recollection in the theta band. J Cogn Neurosci 20:1043–1053.
23. Addante RJ, Ranganath C, Yonelinas AP (2012): Examining ERP correlates of recognition memory: Evidence of accurate source recognition without recollection. Neuroimage 62:439–450.
24. Bergström ZM, Henson RN, Taylor JR, Simons JS (2013): Multimodal imaging reveals the spatiotemporal dynamics of recollection. Neuroimage 68:141–153.
25. Cycowicz YM, Friedman D, Snodgrass JG (2001): Remembering the color of objects: An ERP investigation of source memory. Cereb Cortex 11:322–334.

26. Johansson M, Mecklinger A (2003): The late posterior negativity in ERP studies of episodic memory: action monitoring and retrieval of attribute conjunctions. Biol Psychol 64:91–117.
27. Rugg MD, Curran T (2007): Event-related potentials and recognition memory. Trends Cogn Sci 11:251–257.
28. Hertel PT (1997): On the contributions of deficent cognitive control to memory impairments in depression. Cogn Emot 11:569–583.
29. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, *et al.* (1998): The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59:22–33.
30. Beck AT, Steer RA, Brown GK (1996): Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corportation.
31. Watson D, Weber K, Assenheimer JS, Clark LA, Strauss ME, McCormick RA (1995): Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. J Abnorm Psychol 104:3–14.
32. Treynor W, Gonzalez R, Nolen-hoeksema S (2003): Rumination reconsidered: A psychometric analysis. Cogn Ther Res 27:247–259.
33. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ (1989): The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Res 28:193–213.
34. Holdnack HA (2001): Wechsler Test of Adult Reading: WTAR. San Antonio, TX: Psychological Corporation.
35. Peirce JW (2008): Generating stimuli for neuroscience using PsychoPy. Front Neuroinform 2:10.
36. Reitman JS, Higman B, Lifson A, Rosenblum J (1974): Without surreptitious rehearsal, information in short-term memory decays I. J Verb Learn Verb Behav 13:365–377.
37. Starns JJ, Hicks JL (2005): Source dimensions are retrieved independently in multidimensional monitoring tasks. J Exp Psychol Learn Mem Cogn 31:1213–1220.
38. Coltheart M (1981): The MRC psycholinguistic database. Q J Exp Psychol Sect A 33:497–505.
39. R Core Team (2017): R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Available at: http://www.R-project.org/. Accesssed May 1, 2017.
40. Singmann H, Bolker B, Westfall J, Aust F (2016): afex: Analysis of factorial experiments. R package version 0.16-1.
41. Lenth RV (2016): Least-squares means: The R package lsmeans. J Stat Softw 69:1–33.
42. Delorme A, Makeig S (2004): EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134:9–21.
43. Lopez-Calderon J, Luck SJ (2014): ERPLAB: An open-source toolbox for the analysis of event-related potentials. Front Hum Neurosci 8:213.
44. Dobbins IG, Wagner AD (2005): Domain-general and domain-sensitive prefrontal mechanisms for recollecting events and detecting novelty. Cereb Cortex 15:1768–1778.
45. Han S, O'Connor AR, Eslick AN, Dobbins IG (2012): The role of left ventrolateral prefrontal cortex during episodic decisions: Semantic elaboration or resolution of episodic interference? J Cogn Neurosci 24:223–234.
46. Simons JS, Owen AM, Fletcher PC, Burgess PW (2005): Anterior prefrontal cortex and the recollection of contextual information. Neuropsychologia 43:1774–1783.
47. Cohen MX (2014): Analyzing Neural Time Series Data. Cambridge, MA: MIT Press.
48. Friedman D, Cycowicz YM, Bersick M (2005): The late negative episodic memory effect: The effect of recapitulating study details at test. Brain Res Cogn Brain Res 23:185–198.
49. McDermott CM, LaHoste GJ, Chen C, Musto A, Bazan NG, Magee JC (2003): Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. J Neurosci 23:9687–9695.
50. Vecsey CG, Baillie GS, Jaganath D, Havekes R, Daniels A, Wimmer M, *et al.* (2009): Sleep deprivation impairs cAMP signalling in the hippocampus. Nature 461:1122–1125.
51. Yang RH, Hou XH, Xu XN, Zhang L, Shi JN, Wang F, *et al.* (2011): Sleep deprivation impairs spatial learning and modifies the hippocampal theta rhythm in rats. Neuroscience 173:116–123.
52. Gilmore AW, Nelson SM, McDermott KB (2015): A parietal memory network revealed by multiple MRI methods. Trends Cogn Sci 19:534–543.
53. Wagner AD, Shannon BJ, Kahn I, Buckner RL (2005): Parietal lobe contributions to episodic memory retrieval. Trend Cogn Sci 9:445–453.
54. Sestieri C, Corbetta M, Romani GL, Shulman GL (2011): Episodic memory retrieval, parietal cortex, and the default mode network: Functional and topographic analyses. J Neurosci 31:4407–4420.
55. Kim H (2010): Dissociating the roles of the default-mode, dorsal, and ventral networks in episodic memory retrieval. Neuroimage 50:1648–1657.
56. Rugg MD, Vilberg KL (2013): Brain networks underlying episodic memory retrieval. Curr Opin Neurobiol 23:255–260.
57. Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, *et al.* (2014): Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science 345:1054–1057.
58. Nilakantan AS, Bridge DJ, Gagnon EP, VanHaerents SA, Voss JL (2017): Stimulation of the posterior cortical-hippocampal network enhances precision of memory recollection. Curr Biol 27:465–470.
59. Bonnì S, Veniero D, Mastropasqua C, Ponzo V, Caltagirone C, Bozzali M, Koch G (2015): TMS evidence for a selective role of the precuneus in source memory retrieval. Behav Brain Res 282:70–75.
60. Ye Q, Zou F, Lau H, Hu Y, Kwok SC (2018): Causal evidence for mnemonic metacognition in human precuneus. J Neurosci 38:6379–6387.
61. Dehaene S, Piazza M, Pinel P, Cohen L (2003): Three parietal circuits for number processing. Cogn Neuropsychol 20:487–506.
62. Mizuhara H, Wang LQ, Kobayashi K, Yamaguchi Y (2004): A long-range cortical network emerging with theta oscillation in a mental task. Neuroreport 15:1233–1238.
63. Fingelkurts AA, Fingelkurts AA, Rytsälä H, Suominen K, Isometsä E, Kähkönen S (2006): Composition of brain oscillations in ongoing EEG during major depression disorder. Neurosci Res 56:133–144.
64. Fingelkurts AA, Fingelkurts AA (2015): Altered structure of dynamic electroencephalogram oscillatory pattern in major depression. Biol Psychiatry 77:1050–1060.
65. Fingelkurts AA, Fingelkurts AA, Rytsälä H, Suominen K, Isometsä E, Kähkönen S (2007): Impaired functional connectivity at EEG alpha and theta frequency bands in major depression. Hum Brain Mapp 28:247–261.
66. Gonzalez A, Hutchinson JB, Uncapher MR, Chen J, LaRocque KF, Foster BL, *et al.* (2015): Electrocorticography reveals the temporal dynamics of posterior parietal cortical activity during recognition memory decisions. Proc Natl Acad Sci U S A 112:11066–11071.
67. Staresina BP, Fell J, Do Lam AT, Axmacher N, Henson RN (2012): Memory signals are temporally dissociated in and across human hippocampus and perirhinal cortex. Nat Neurosci 15:1167–1175.