**An ERP Study of Source Memory in Unipolar Depression**

Elyssa M. Barrick and Daniel G. Dillon

Number of words:

Number of figures:

Number of tables:

Supplemental information: none

Keywords:

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:** Major Depressive Disorder (MDD) is associated with poor memory but the underlying mechanisms are not well understood. Memory retrieval depends on the hippocampus and frontal lobes, and MDD is characterized by hippocampal volume loss and hypofrontality. Therefore, retrieval failures may contribute to poor memory in depression. We used event-related potentials (ERPs) to investigate this hypothesis.

**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 (cognitive source). The electroencephalogram was recorded as participants recalled the perceptual and cognitive source of each word.

**Results:** Memory in depressed adults was generally less confident and less accurate than in controls. However, depressed adults showed excellent cognitive source memory for words from the mobility task. Behavior was paralleled by the ERPs: depressed adults showed weaker left parietal activity except when retrieving the cognitive source of words from the mobility task. Furthermore, controls generated a late negative potential that was focused over frontal and posterior scalp during cognitive and perceptual retrieval, respectively, but in MDD this potential was diffuse and extended to frontal scalp in all conditions.

**Conclusions:** Depressed adults showed impaired memory, weak left parietal activity, and diffuse frontal activity. However, accuracy and left parietal activity were rescued by the combination of deep encoding in the mobility task and cognitive source retrieval. Thus, retrieval deficits may contribute to poor memory in MDD, but depressed adults can perform well provided information is deeply encoded and attention is carefully focused during retrieval.

**Introduction**

**Materials and Methods**

**Participants**

Participants were recruited from the community and compensated $25/hour. All were 18-62 years old, right-handed, with no history of neurological disorders or unstable medical conditions. Informed consent was obtained with a protocol approved by the Partners HealthCare Human Research Committee. To determine eligibility, participants were screened over the phone or via a web-based instrument. The screen . . . [briefly describe the criteria used to select subjects; make sure to mention lack of medication for MDD] . . . Based on the screen, X healthy and Y depressed adults were invited to complete the ERP session.

To confirm that the screening was accurate, immediately after each ERP session psychiatric history was assessed with the MINI International Neuropsychiatric Interview, version 6.0 (Sheehan et al., 1998), and the Beck Depression Inventory II (BDI-II; Beck, Steer, & Brown, 1996) was administered. Data from depressed participants (*n* = X) were retained if they met criteria for MDD but no other DSM-IV Axis I diagnosis, with the exceptions of secondary generalized anxiety, social anxiety, or specific phobia, and provided they had a BDI-II score ≥ 14. Data from healthy individuals (*n* = Y) were retained if they reported no current or past psychiatric illness. Finally, data from X depressed and Y healthy individuals were excluded due to excessive EEG artifacts (see section *EEG pre-processing*). Thus, the final sample consisted of 24 unmedicated adults with MDD and 24 controls.

**Self-report Measures**

In addition to the BDI-II, participants completed the Mood and Anxiety Symptom Questionnaire(MASQ; Watson et al., 1995), the Ruminative Response Scale (RRS; Treynor, Gonzalez, & Nolen-hoeksema, 2003), and the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) (PSQI). The MASQ includes separate scales for . . . The RRS yields measures of brooding, reflection . . . The PSQI is a . . . Finally, the Wechsler Test of Adult Reading (WTAR; Holdnack, 2001) was used as a brief assessment of IQ. We included these measures to characterize the MDD sample and to determine whether any deficits associated with depression could be related to a more narrowly defined process (e.g., brooding rumination).

**Task**

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

**Stimuli.** Over the course of 100 encoding trials participants made animacy and mobility judgments for individual words. Therefore, we selected 100 words from **X**, with 25 words from each of 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*). One-way analyses of variance (ANOVA) found no significant differences among the lists for number of letters per word (mean±S.D. = 5.27±1.29), number of syllables (1.52±0.50), frequency of occurrence (35.58±79.02), concreteness (598.87±20.18), or imageability (596.80±25.31), all *ps* > 0.064. Emotionally neutral words were selected to avoid effects associated with mood congruent encoding or retrieval (G H Bower, 1981; Gordon H. Bower, 1987) and thus isolate the cognitive impact of depression on retrieval. Word lists are printed in the appendix.

**Encoding.** The task included six encoding-retrieval cycles. Each encoding block consisted of 16 trials in which a word appeared on the left or right side of the screen directly above one of two questions: “Living/Nonliving?” (animacy judgment) or “Mobile/Immobile?” (mobility judgment) (duration: 3.5 s). Participants responded to each question by pressing a button corresponding to the correct answer. Thus, each word was encoded in relationship to a perceptual source defined by screen position (left or right) and a conceptual source defined by the encoding task (animacy vs. mobility judgment). Each block included four words from every category (living/immobile, non-living/immobile, living/mobile, non-living/mobile), each of which was assigned to one of the four encoding conditions defined by screen position and task (left/animacy, right/animacy, left/mobility, right/mobility).

Immediately after each encoding block, a 3-digit number (262, 931, 888, 704, 557, or 474) was centrally presented for 30 s and participants were asked to count backwards in steps of three, out loud. This task was used to disrupt sub-vocal rehearsal, clear working memory, and thus increase the difficulty of the upcoming retrieval test (Reitman, Higman, Lifson, & Rosenblum, 1974). To minimize stress during counting, participants were told to strive for accuracy but, in case of a mistake, to simply proceed as though no error had been committed. The experimenter observed the counting but no data were collected during this task.

**Retrieval.** Each retrieval block comprised 48 trials that included a cue, word, and response screen. On 32 trials, the cue was “Side?” or “Question?” (16 trials each) and the word came from the immediately preceding encoding block. These cues prompted retrieval of the perceptual (“On what side of the screen did this word appear?”) and conceptual (“What question did I answer for this word?’) sources, respectively. On the remaining 16 trials, the cue was “Odd/Even?” the word was a numeral between “one” and “ninety-six”, and the participant was asked to judge parity. The “Odd/Even?” trials were intended as a control condition: participants had to read the cue, interpret it, and retrieve information from memory before responding, but—in contrast to the “Side?” and “Question?” cues—the “Odd/Even?” cue prompted retrieval from semantic rather than episodic memory. Therefore, comparing ERP data from “Side?” and “Question?” trials relative to “Odd/Even?” trials should isolate activity specific to episodic retrieval. Cues were printed directly above the words, and the presentation order of the words and cues was randomized.

The response screen consisted of the word ‘RESPOND’ printed above the word and the numbers 1-5 printed below. The numbers corresponded to response options indicating the participant’s choice and level of confidence in that choice: 1 = high confidence (*left* or *living/non-living* or *odd*), 2 = low confidence (*left* or *living/non-living* or *odd*), 3 = guess, 4 = low confidence (*right* or *mobile/immobile* or *even*), 5 = high confidence (*right* or *mobile/immobile* or *even*). Labels indicating the meaning of each response were printed below the numbers. Participants were instructed to select “guess” when they were unable to retrieve any information.

Each cue appeared for 1 s and was then joined by the word, which remained visible along with the cue for 3 s. At this point the response screen was presented and remained onscreen until the participant pressed a button or 10 s had elapsed. Cues were displayed before words because we anticipated time-locking the EEG data to the word onsets in order to study source retrieval. By presenting the cues first, we aimed to allow participants sufficient time to prepare a search strategy such that they could engage in retrieval as soon as each word appeared, increasing the likelihood that our ERP analysis would capture retrieval rather than preparation for retrieval. Similarly, we delayed the response screen in order to reduce the effect of motor preparation on the ERPs to words, and we allowed participants 10 seconds to respond in case of global slowing in MDD. Finally, a centrally presented fixation cross was continuously visible throughout retrieval, and the cues and words were presented directly above and below fixation, respectively, such that participants could see all the stimuli without needing to move their eyes. A jittered inter-trial interval (500-2000 ms) separated the trials.

**Procedure.** Following application of the EEG net, participants were given detailed instructions. For the mobility task, participants were instructed to respond “mobile” if the word described an object whose primary purpose was to move (e.g., car) or that could move under its own power (e.g., dog); otherwise, they were told to respond “immobile”. Next, participants completed a practice cycle with four encoding and ten retrieval trials (four “Side?” four “Question?” and two “Odd/Even?”). Thus, participants knew their memories would be tested.

**EEG Recording**

The EEG was recorded with a 128-sensor HydroCel GSN Electrical Geodesics Inc. (EGI) net connected to a Net Amps 300 amplifier (sample rate = 1000 Hz, 0.02–100 Hz bandpass filter). Data were referenced to the vertex during acquisition. Impedances were kept below 45 kΩ when possible; none exceeded 75 kΩ. EEG data were acquired during retrieval.

**Behavioral Data Analysis**

In order to isolate effects of depression on retrieval one must account for other factors that can influence memory, including age (Cabeza et al., 2004; Mark & Rugg, 1998), depth of encoding (Craik & Tulving, 1975), and the influence of different recognition cues (Konkel, Selmeczy, & Dobbins, 2015; Marsh & Hicks, 1998). Moreover, because depression is more prevalent in women it is important to consider gender (Nolen-Hoeksema, 2001). Therefore, we analyzed the behavioral data using linear mixed models implemented with the R (R Developement Core Team, 2015) library *lme4* (Bates, Maechler, Bolker, & Walker, 2015), as these can account for covariates more easily than conventional ANOVAs. The specific models used for each dependent variable are described below, but in each case we computed an initial model with task elements (e.g., encoding task, recognition cue) and covariates (age, gender) as fixed effects but with *Group* omitted. Next, we computed another model including *Group*, either as a main effect or in interaction with other factors, and then used likelihood ratio tests implemented in the R library *anova* to compare model fits by chi-square test. If the second model was a significant improvement on the first model, we report its parameters; otherwise, we report parameters from the first model. All models used *word* and *subject* as random effects, for which we modeled intercepts but did not adjust slope. When modeling encoding accuracy (coded 0 or 1), we used glmer with the logit link function. Finally, we extracted *p*-values for parameters from the best-fitting models using the R library *lmerTest*.

**Encoding**. Prior to statistical analysis, we dropped trials with no response or where RT exceeded the participant’s mean±3SD; fewer than 1% of trials were dropped. We analyzed accuracy (did the participant answer the encoding question correctly?) and RT. Our first accuracy model included *Task* (animacy vs. mobility judgment), *Side* (left, right), *Block* (1-6), *Gender*, and *Age* as fixed effects. Our first RT model included the same factors plus *Accuracy*. We compared these to models that included *Group* as an additional fixed effect.

**Retrieval**. We dropped trials with no response or where RT exceeded the participant’s mean±3SD; fewer than 2% of trials were dropped. Next we analyzed the “Odd/Even?” trials, which were only included to serve as a control condition for the ERP analysis.Accuracy (percent correct) on “Odd/Even?” trials was at ceiling (controls: 98.43±0.12; MDD: 99.13±0.09), and RT (in ms) was similar between the groups (controls: 862.58±51; MDD: 779.00±48). Adding *Group* did not improve models that included *Block, Age*, and *Gender* as factors, χ2s < 2.1, *p*s > 0.14, indicating that depression did not affect performance in this condition and underscoring its suitability as a control.

For the remaining trials, we conducted separate analyses for accuracy and confidence. Accuracy was coded as follows: incorrect, high confidence = 1; incorrect, low confidence = 2; guess = 3; correct, low confidence = 4; correct, high confidence = 5. Confidence was treated as orthogonal to accuracy and was coded: guess = 1, low confidence = 2, high confidence = 3. We computed three models for accuracy and confidence. The first included *Block*, *Cue* (“Side?” vs. “Question”), *Encoding Task* (animacy, mobility), *Encoding Side* (left, right), *Age*, and *Gender*. The second model added a *Cue* x *Encoding Task* interaction, and the third added a *Group* x *Cue* x *Encoding Task* interaction, which automatically added the main effect and all two-way interactions involving *Group*. We used similar models to analyze for RT on correct trials.

**ERP Analysis**

**Pre-processing.** Off-line analyses were conducted with the EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) toolboxes for MATLAB (MathWorks, Natick). EEG data from the retrieval blocks were merged and re-referenced to the average of all electrodes prior to bandpass filtering from 0.1 to 30 Hz in EEGLAB. Bad channels were visually identified and interpolated. We set an *a priori* cut-off of up to 18 bad channels (14% of the total); datasets that exceeded this cut-off were excluded from further analysis (controls, *n* = **X**; MDD, *n* = **Y**). Next, data marked by gross artifacts were manually removed and independent component analysis was used to extract components capturing blinks, HEOG, and EKG. Using ERPLAB, the cleaned data were time-locked to word onsets and segmented from 200 ms pre-stimulus to 2000 ms post-stimulus; the pre-stimulus interval was used for baseline correction. Next, a moving window peak-to-peak function flagged segments where the difference between the minimum and maximum voltage (computed over 200 ms intervals with a 100 ms sliding window) exceeded 100 μV. Any segment with extreme values (+/- 100 μV) was also flagged. Finally, the data were visually inspected to ensure that all artifacts were marked, and then the artifacts were rejected. Datasets with artifacts on more than 50% of trials were excluded (controls, *n* = **X**, MDD, *n* = **Y**).The cleaned, segmented data were then averaged into bins defined by encoding position, encoding task, recognition cue, and recognition accuracy (e.g., encoded on left + animacy judgment + Side cue + recognition hit).

**Group-level analyses**. Will pin down the behavioral results first as that will inform what gets presented here . . . \*DD note to self: complement the classic ERPs with trial-level analysis focused on 400-800 left parietal, maybe also right parietal (and right frontal + LPN)

**Results**

**Demographics**

As shown in Table 1, there were no group differences for gender, age, or education. As expected, the MDD group endorsed more depression and anxiety than the controls, with the mean BDI-II score indicating moderate depression. The MDD group also reported more rumination and poorer sleep, but there was no difference in IQ as estimated from WTAR scores.

PLEASE INSERT TABLE 1 ABOUT HERE

**Behavior**

**Encoding**. Encoding behavior was not affected by depression but it was influenced by the task: the mobility judgment was more difficult than the animacy judgment. This was evident in percent correct (mobility: 92.42±0.26; animacy: 95.85±0.20; *Z* = -4.91, *p* < 0.001) and RT (mobility = 1,801±552 ms; animacy = 1,664±535 ms; *Z* = 10.54, *p* < 0.001). Participants responded more quickly when making correct (1,720±541 ms) vs. incorrect (1,923±619 ms) judgments, *Z* = -3.46, *p* < 0.001, and RT decreased over the session (negative linear *Block* effect, *Z* = -6.34, *p* < 0.001). Notably, the addition of *Group* did not improve the accuracy or the RT model, χ2s < 1.93, *p*s > 0.16. Thus, depressed and healthy adults performed similarly at encoding and the mobility judgment was more difficult than the animacy judgment.

**Recognition accuracy**. The percentages of responses of each type (hit, miss, guess) as a function of retrieval cue, encoding task, and group are given in Table 2.Figure 1A shows that depressed adults were less accurate than controls except for words encoded in the mobility task and presented under the “Question?” cue. The figure also depicts a cue by task interaction: under the “Question?” cue, participants responded more accurately to words from the mobility vs. animacy task, whereas responses to the “Side?” cue were insensitive to the encoding task.

These impressions were captured by the linear models, which were improved by the addition of *Group*, χ2 = 26.40, *p* < 0.001. The best-fitting model included a *Group* x *Cue* x *Encoding Task* interaction, *Z* = -2.13, *p* = 0.033, which subsumed significant *Cue* x *Encoding Task* and *Group* x *Encoding Task* interactions as well as significant main effects of *Cue* and *Encoding Task* (*Z*s > 2.7, *p*s < 0.006). Two sets of follow-up analyses unpacked the interaction. First, pairwise comparisons confirmed that depressed adults were more accurate than controls when responding to words from the mobility task presented under the “Question?” cue, *Z* = 1.98, *p* = 0.048. In all other cells the controls were more accurate than the MDD group, although the difference was never significant (*Z*s < 1.63, *p*s > 0.10). Second, breaking down the data by cue type revealed a significant *Group* x *Encoding Task* interaction for responses to the “Question?” cue, *Z* = 3.25, *p* = 0.001: both groups responded more accurately to words from the mobility vs. animacy task, but the difference was larger in depressed (*Z* = 9.21, *p* < 0.001) vs. healthy (*Z* = 4.62, *p* < 0.001) participants, leading to the interaction. By contrast, the *Group* x *Encoding Task* interaction was not significant for responses to the “Side?” cue, *Z* = 0.57, *p* = 0.57, as both groups were able to retrieve side information equally well for words from both encoding tasks. Finally, the best-fitting model revealed effects of *Age*, *Z* = -3.31, *p* < 0.002, and *Gender*, *Z* = 3.32, *p* < 0.002, as well as a linear *Block* effect*, Z* = 3.23, *p* = 0.001. Thesereflected higher accuracy in younger vs. older adults, in men vs. women, and in later vs. earlier blocks, respectively.

PLEASE INSERT FIGURE 1 AND TABLE 2 ABOUT HERE

**Recognition confidence**. The confidence data shown in Figure 1B indicate that depressed adults were less confident than controls, with the difference most pronounced under the “Side?” cue. Consistent with this impression, the model was improved by the addition of *Group*, χ2 = 18.46, *p* = 0.001, and included a trend for a *Group* x *Cue* interaction, *Z* = -1.65, *p* = 0.098. The interaction reflected the fact that while the controls were generally more confident than the depressed adults, the group difference was stronger under the “Side?” cue, *Z* = 2.42, *p* = 0.016, than under the “Question?” cue, *Z* = 1.14, *p* = 0.255. The model also revealed strong effects of *Cue*, *Z* = -5.33, *p* < 0.001 and *Encoding Task*, *Z* = 2.91, *p* = 0.004, as well as a positive linear effect of *Block*, *Z* = 3.69, *p* < 0.001. These results reflect the fact that participants were more confident when responding to the “Question?” cue vs. the “Side?” cue, when responding to words encoded in the mobility vs. the animacy task, and when responding in later vs. earlier retrieval blocks. In contrast to accuracy, confidence was not affected by *Age* or *Gender*.

**Recognition RT**. Figure 1C shows that correct RT was similar across the groups, with all participants noticeably slower in response to the “Question?” vs. “Side?” cue. This impression was confirmed by the linear modeling, which was not improved by the addition of *Group*, *p =* 0.08, but revealed a strong effect of *Cue*, *Z* = -45.51, *p* < 0.001. There was also a negative linear effect of *Run*, *Z* = -18.82, *p* < 0.001, a strong effect of *Confidence*, *Z* = 21.61, *p* < 0.001, and an effect of *Gender*, *Z* = -3.09, *p* = 0.003. These reflected shorter correct RTs in later vs. earlier blocks, for high vs. low confidence responses, and in males vs. females.

**Summary**. Depression affected source memory: compared to controls, depressed adults were less confident and less accurate. However, the group difference in accuracy was modest and it reversed when words from the mobility task were presented under the “Question?” cue. At encoding, the mobility task was associated with lower accuracy and longer reaction times, suggesting that it engendered deeper processing than the animacy task (Craik & Tulving, 1975); in other words, it appears that participants had to think more carefully about the referent of the word, for longer, when making mobility vs. animacy judgments. Thus, the retrieval data are consistent with a negative effect of depression on source memory that disappears provided encoding is deep and the retrieval cue directs attention to the cognitive operations performed at study. This pattern is predicted by the cognitive initiative framework, which argues that depressed adults perform poorly in unconstrained environments but can display excellent memory if their attention is focused at both encoding and retrieval (Hertel, 1997).

**ERPs**

Figure 2 displays topographic maps of correct responses to the “Question?” “Side?” and “Odd/Even?” prompts. In both groups, the two most commonly observed ERPs elicited during successful retrieval are readily apparent. From 400-800 ms, there is robust activity over parietal electrode sites that is stronger over the left vs. right hemisphere in controls; this potential has been consistently associated with recollection (Rugg & Curran, 2007). From 800-2000 ms, a positive potential is evident over right frontal cortex. This potential was originally thought to reflect post-retrieval monitoring—examining what has been extracted from memory to determine whether or not it meets the retrieval goal—but subsequent studies found that this potential (and activation of the right dorsolateral prefrontal cortex) is not specific to episodic retrieval but can be elicited during semantic retrieval and decision-making more generally (Fleck, Daselaar, Dobbins, & Cabeza, 2006; Hayama, Johnson, & Rugg, 2008; Hayama & Rugg, 2009). To that point, the late right frontal potential is clearly evident even during “Odd/Even?” judgments. Finally, a late negative potential is also apparent in these data during the same time window (800-2000 ms) as the right frontal effect but originating over the occipital scalp and extending over left frontal cortex, particularly during successful responses to the “Question?” prompt. This late posterior negativity (LPN) was reported in early studies of source memory (Cycowicz, Friedman, & Snodgrass, 2001) but has generally received less attention in the literature.

The topographies from healthy and depressed adults were broadly similar but one difference was immediately apparent: parietal activity from 400-800 ms appeared to be markedly weaker in the MDD group. To determine whether this visual impression was reliable, we extracted the mean ERP amplitude between 400-800 ms from four parietal electrodes in the left (P1, P3, P5, P7) and right (P2, P4, P6, P8) hemispheres and submitted them to a *Group* x *Condition* (Question, Side, Odd/Even) x *Hemisphere* ANOVA. Indeed, this analysis returned a main effect of *Group*, *F*(1,46) = 4.35, *p* = 0.043, reflecting decreased activity in depressed vs. healthy adults. There was also a main effect of *Condition*, with follow-up tests using the REGWQ procedure yielding reliable differences between all three conditions (Question > Side > Odd/Even, all *ps* < 0.043). This group difference is also readily apparent in the waveforms, which are plotted in Figure 3.

PLEASE INSERT FIGURES 2 AND 3 ABOUT HERE

**Difference waves**. In order to better isolate the effect of MDD on source retrieval and forge links between the ERPs and behavior, we next created difference waves by subtracting activity on correct Odd/Even trials from activity in the four bins formed by crossing the encoding tasks with the two retrieval cues. Figure 4 shows topographic maps of these difference waves.

**Next thing to do is create Figures 3 and 4 . . .**

**\***Okay, so I ran the stats on the left/right parietal effects from 400-2000 (posterior electrodes capture the effect better), and the bottom line is that there are nice effects of Condition and Latency in the left hemi but no effect of Group. Thus, if you show these data you should probably show them averaged over group (I made a PDF for that). In the right hemi there are Condition effects fro 400-800 along with a smaller effect from 800-1200, but again there is no group effect here. Definitely worth showing and noting but it does not back up my hunch that we’d see a Group x Condition interaction with sustained activity only in Q/MI for MDDs . . .

Waveforms focus on the 400-800 ms positive deflection associated with recollection, controls show strong separation for hits in all cells formed by Cue x Task relative to number hits. By contrast, this component was notably weaker in depressed and showed less separation from number hits. To identify neural activity specifically associated with source retrieval, we subtracted activation on number hit trials from activation in all other cells and plotted topographic maps of the difference waves. These maps revealed strong activity over parietal sites in response to the “Question?” vs. “Side?” cue, with the “Side?” cue eliciting relatively more fronto-central activation. Compared to controls the depressed adults showed weaker parietal activation . . . I’m not 100% convinced myself, keep plugging away. Hang on, I see that the left parietal activation stays on throughout the recording epoch in all cells for controls but really only in the Question/mobility cell in MDDs. Let’s do Group x Cell (4) x Time (4-8,8-12,12-16,16-19).

When I look at the diff wave topos from 400-2000, the right frontal effect is less obvious. Is that because it’s there for the number hits too? Yes, judging from my powerpoint that’s the case. But the LPN is very obvious and it has a neat property, at least in controls: it looks like it’s constrained to occipital sites under Side but extends up to left PFC under Question. In the MDD group this is less true—the LPN is broader in them. So you might say that the MDD group shows generally weaker parietal activation except for Q/MI and that while the controls appear, speculatively, to be reactivating relevant circuits, this seems like it may be less so for MDD.