Published in final edited form as:

J Int Neuropsychol Soc. 2016 April ; 22(4): 412–425. doi:10.1017/S1355617716000023.

Decreased Fronto-Limbic Activation and Disrupted Semantic-Cued List Learning in Major Depressive Disorder

Michelle T. Kassel^{1,2}, Julia A. Rao¹, Sara J. Walker², Emily M. Briceño^{2,3}, Laura B. Gabriel¹, Anne L. Weldon¹, Erich T. Avery², Brennan D. Haase², Marta Peciña², Ciaran M. Considine², Douglas C. Noll², Linas A. Bieliauskas², Monica N. Starkman², Jon-Kar Zubieta², Robert C. Welsh², Bruno Giordani², Sara L. Weisenbach^{1,2,4}, and Scott A. Langenecker^{1,2}

¹University of Illinois at Chicago, Department of Psychiatry

²University of Michigan Medical Center, Department of Psychiatry

³Ann Arbor VA Medical Center

⁴Jesse Brown VA Medical Center, Research & Development

Abstract

Objective—Individuals with Major Depressive Disorder (MDD) demonstrate poorer learning and memory skills relative to never-depressed comparisons (NDC). Previous studies report decreased volume and disrupted function of frontal lobes and hippocampi in MDD during memory challenge. However, it has been difficult to dissociate contributions of short-term memory and executive functioning to memory difficulties from those that might be attributable to long-term memory deficits.

Method—Adult males (MDD, n=19; NDC, n=22) and females (MDD, n=23; NDC, n=19) performed the Semantic List Learning Task (SLLT) during fMRI. The SLLT Encoding condition consists of 15 lists, each containing 14 words. After each list, a Distractor condition occurs, followed by cued Silent Rehearsal instructions. Post-scan recall and recognition were collected. Groups were compared using block (Encoding-Silent Rehearsal) and event-related (Words Recalled) models.

Results—MDD displayed lower recall relative to NDC. NDC displayed greater activation in several temporal, frontal, and parietal regions, for both Encoding-Silent Rehearsal and the Words Recalled analyses. Groups also differed in activation patterns in regions of the Papez circuit in planned analyses. The majority of activation differences were not related to performance, presence of medications, presence of comorbid anxiety disorder, or decreased gray matter volume in MDD.

Conclusions—Adults with MDD exhibit memory difficulties during a task designed to reduce the contribution of individual variability from short-term memory and executive functioning processes, parallel with decreased activation in memory and executive functioning circuits.

*Corresponding Author: Scott A. Langenecker, University of Illinois at Chicago, Department of Psychiatry, 1601 W. Taylor St. M/C 912 Chicago, IL 60612, Phone: 312-996-0085, slangenecker@psych.uic.edu.

The authors report no conflicts for this work.

Ecologically valid long-term memory tasks are imperative for uncovering neural correlates of memory performance deficits in adults with MDD.

Keywords

memory; depression; list learning; fMRI; serial position; hippocampus

Introduction

Memory Problems in Major Depressive Disorder

Major Depressive Disorder (MDD) is the leading cause of disability in the United States for individuals between the ages of 15 and 44 (World Health Organization, 2008), and memory complaints are one of the most common symptoms reported by patients with MDD. A large corpus of research demonstrates that memory difficulties are present in MDD, unrelated to poor effort or lack of engagement (Ashendorf, Constantinou, & McCaffrey, 2004; Bora, Harrison, Yücel, & Pantelis, 2013; Considine, et al., 2011; Hermens, Naismith, Redoblado-Hodge, Scott, & Hickie, 2010; Milne, MacQueen, & Hall, 2012; Rees, Tombaugh, & Boulay, 2001; Roberson-Nay et al., 2006). Particular types of memory, such as explicit memory, but not implicit memory, have been shown to be differentially affected in MDD (Elderkin-Thompson, Moody, Knowlton, Hellemann, & Kumar, 2011; Mulligan, 2011). Meta-analyses suggest that episodic memory may be most affected for individuals with MDD (Liu, Li, Xiao, Yang, & Jiang, 2013; Riggs, Carr, Bogue, & Dooley, 2005) revealing moderate effect sizes on verbal list learning, recall, and working memory tasks (Bora et al., 2013). Individuals with MDD have also been shown to exhibit relatively preserved encoding and retention, although these studies are typically in comparison to individuals with mild cognitive impairment and dementia (Langenecker, Lee, & Bieliauskas, 2009, Snyder 2013).

Despite substantial literature documenting memory impairment in depression, mechanisms for these disruptions have not converged on clearly defined neural networks. Some studies suggest that memory dysfunction is linked to abnormalities in the limbic hypothalamic-pituitary-adrenal axis resulting from chronic elevated cortisol levels potentially causing cell death or dendritic atrophy, primarily in hippocampal regions (Lee, Ogle, & Sapolsky, 2002; McEwen, Magariños, & Reagan, 2002; Sapolsky, 2000). Other evidence attributes memory dysfunction in MDD to greater duration of untreated MDD, as repeated untreated episodes are associated with greater hippocampal volume loss (Sheline, Gado, & Kraemer, 2003). Others suggest that MDD poses a constant distractor, diminishing attentional resources that might otherwise be available to assist with memory encoding and retrieval (Langenecker et al., 2009; Watkins & Brown, 2002). In theory, attentional distraction reduces the capacity for attentional focus on soon-to-be encoded information, and is thought to be mediated by fronto-parietal cognitive control networks. Additionally, some studies posit that effortful memory processes are disrupted during MDD, whereas automatic processes remain relatively intact, although there are conflicting results supporting that hypothesis (Rohling & Scogin, 1993). These disparate theories suggest that careful research is still needed to understand the neural structures and networks associated with memory problems in MDD. This is further complicated by the fact that memory may involve multiple processes,

including executive functioning (EF), and is easily degraded by distraction, poor sustained attention, slow processing speed, and disrupted organizational skills (Rogers et al., 2004).

The neural structures and circuits supporting memory are well known and have been extensively studied outside of MDD (Kim, 2011; Squire, 1992), including the Papez circuit, comprised of limbic structures such as the hippocampus, mammillary bodies and cingulate gyrus (Papez, 1937), as well as fronto-parietal networks involved in EF and short-term memory (STM). Structural imaging studies of memory in MDD have demonstrated perturbation of frontal lobes and hippocampi, regions that facilitate memory encoding and recall. Smaller hippocampal volume in MDD has also been widely reported (Bremner et al., 2000; Kempton et al., 2011; MacQueen, Yücel, Taylor, Macdonald, & Joffe, 2008; MacQueen, & Frodl, 2011), as well as smaller thalamus, overall frontal lobe, and orbitofrontal cortex (Kempton et al., 2011). Similar findings in MDD were reported in another meta-analysis, indicating abnormalities in cortico-striatal-pallidal-thalamic circuits, critical for attention, memory encoding, and retention (Bora, Harrison, Davey, Yücel, & Pantelis, 2012).

Although fewer in number, functional imaging studies have started to examine whether the aforementioned structural differences might be extended to decreased functional capacity and efficiency in MDD. Decreased hippocampal, amygdala, and anterior cingulate cortex activation during verbal memory tasks have been observed in MDD (Bremner, 2004; Milne et al., 2012). Specifically, healthy individuals undergoing PET showed greater increases in blood flow in bilateral hippocampi during a word and paragraph memory task, compared to MDD, with no behavioral differences between the groups, nor a correlation between activation and memory (Bremner, 2004). This suggests that individuals with MDD may engage in activities of learning and memory differently, or to a lesser extent than those without MDD. A more recent study reported that hippocampal activation was related to better performance on a paired semantic word matching task, but only in the never-depressed comparisons (NDC; Milne, et al., 2012), suggesting low coupling between activation and performance in the context of MDD. MDD patients also displayed different patterns of activation relative to NDC, in frontal and parietal regions in tasks requiring learning and memory. These and other reports led to the conclusion that integrated and perhaps complimentary fronto-parietal and limbic networks support memory function and may be disrupted in MDD, yet the relationship between disrupted network function and memory deficits remains unclear (Dietsche et al., 2014; Werner et al., 2009).

It is difficult to translate the rather specific way that memory is measured in most neuropsychological probes to the neuroimaging environment. Recall, and not recognition, is often considered the more prototypic pattern of impairment in MDD, yet verbal recall is avoided in neuroimaging environments to reduce the likelihood of head motion. Furthermore, memory probes are often multifaceted with a heavy EF load for organization and encoding strategies during learning and retrieval. This traditional task design makes memory tasks more ecologically valid, but also, unfortunately, results in a more balanced contribution of these multifactorial processes. To better understand the memory challenges that individuals with MDD may face, it is valuable to utilize a memory task that targets

memory systems more heavily, retains external validity, and has sensitive performance characteristics to allow translation to clinical settings.

We designed a Semantic List Learning Task (SLLT) as a more targeted probe of memory processes in depression employing two distinct strategies to reduce the influence of individual variability in STM and EF processes (Langenecker, Caveney, Persad, and Giordani, 2004; Schallmo et al., 2015; Weisenbach et al., 2014a). First, the task uses a Brown-Peterson paradigm to minimize rehearsal of recent words, and thereby diminish the contributions of individual variability in STM processes to overall memory (long-term memory, LTM) performance. In the absence of distraction, STM processes can aid in LTM behavioral performance, potentially compensating for LTM weakness (Brown, 1958; Peterson & Peterson, 1959). Adding a distractor component immediately following the encoding stage of the task requires the participant to shift attention to a separate task, thereby preventing rehearsal of the most recently displayed items, theoretically diminishing STM impact on LTM performance. Second, we provided semantic organizational cues for both encoding and recall to minimize individual differences in EF support (e.g. clustering strategies) in encoding. Variance attributable to individual differences in both EF and STM is minimized in the SLLT design; hence, subsequent individual differences in memory performance will have a relatively large share of individual variability attributable to networks involved in encoding and consolidation of memory. We hypothesized that use of the SLLT would clarify the extent and underlying neural basis of performance difficulties in MDD, including in relation to other traditional neuropsychological measures of attention, EF, and memory. Hypothesis one predicted that individuals with MDD would display poorer memory recall performance compared to NDC. Hypothesis two proposed that the MDD group would have decreased activation in frontoparietal and limbic regions relative to NDC. Hypothesis three investigated whether specific brain activation patterns were predictors of SLLT performance, or potential converging findings between behavioral and activation abnormalities in MDD.

Methods

Participants

All participants were between 18 and 65 years of age. Forty (21 males, 19 females) participants were NDC, and 42 (19 males, 23 females) participants had received a diagnosis of MDD, as confirmed by the diagnostic criteria outlined in the Structured Clinical Interview for DSM-IV (SCID-I; First, Spitzer, & Gibbon, 1995). Participants were also administered the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) and Beck Depression Inventory (BDI) as depression symptom severity measures. See Table 1 for sample demographic and clinical information.

MDD participants with comorbid anxiety disorder ($n = 12$) were eligible for participation, but could have no other previous or current psychiatric comorbidities. Participants were recruited through printed advertisements in the community and a university website designed for recruitment purposes. The Institutional Review Board at the University of Michigan approved the study. All participants provided written informed consent prior to study participation and were compensated up to \$60. Consistent with our prior work

(Langenecker et al., 2007a, Weisenbach et al., 2014a), all participants were screened to ensure they were free of any medical or neurological disorder, contraindications for MRI, uncontrolled hypertension or diabetes, head injury with loss of consciousness greater than five minutes, psychotic symptoms, and current substance use or history of substance dependence within five years of the MRI. All NDC participants had no personal history of psychiatric illness.

Measures

Participants were administered the California Verbal Learning Test – Second edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) as part of a neuropsychological battery completed during the study. Other neuropsychological tests were included to evaluate divergent validity, including the Parametric Go/No-go Test (Votruba and Langenecker, 2013), Wisconsin Card Sort Test (Grant & Berg, 1948), and Trail Making Test (Army Test Battery, 1942).

The SLLT is a learning and memory task conducted during functional Magnetic Resonance Imaging (fMRI) and designed for translation for clinical applications (Schallmo et al., 2015, Weisenbach et al., 2014a). As such, the focus is on defining a robust performance signature to capture differences between NDC and MDD (or other patient groups). The SLLT is comprised of three blocks: Encoding, Distractor, and Silent Rehearsal (Figure 1). The task consists of 15 lists of 14 semantically related words, for a total of 210 words. A semantic category cue is visually provided at the beginning of each list, displayed for 3.5 seconds. Following the category cue, 14 words are displayed on a screen one at a time, for an average display time of 3.5 seconds. The inter-stimulus interval is a 1 to 4 second jittered range, where a fixation cross is displayed. The total time for one Encoding block is typically 58.25 seconds. A distractor task immediately follows the last word of each list. This is the “Go” portion of the Parametric Go/No-go (PGNG) task during which “x”, “y”, and “z” are presented (Langenecker, Zubietta, Young, Akil, & Nielson, 2007b). Each Distractor block lasts for 14 seconds. The Silent Rehearsal block presents participants with the category cue of the previous list, displayed for 14 seconds. The SLLT then repeats the Encoding, Distractor, and Silent Rehearsal blocks for a new category and list of words. There are three lists presented in each run, with five runs total. Lists are randomized within runs, and words and randomized within lists to avoid any order by position by frequency confounds (Schallmo et al., 2015). The SLLT includes a post-scan cued recall task with semantic category cues provided for all 15 lists, as well as a recognition trial.

Procedure

After informed consent was obtained and the SCID-I completed, all participants were administered a brief neuropsychological battery. On a separate day participants underwent the fMRI session employing the SLLT. Prior to entering the scanner, participants were verbally introduced to the SLLT. Participants were told they would see a category cue followed by words within that category, shown one at a time on the screen. They were instructed to read each word silently without moving their lips and to try to remember each word. Participants were then informed that they would complete a reaction time task (Distractor) where they should respond by pressing their index finger any time they see the

letter “x”, “y”, or “z” on the screen, regardless of order of presentation. It was explained that a category cue prompt would appear on the screen instructing the participant to silently recall the words from the current word list. There was a 30-minute delay between the final SLLT run in fMRI and the recall session. Participants were given a recall packet that provided the semantic category cues only, and asked to record any words that they could remember from each of the categories.

MRI Acquisition

Whole brain imaging was performed using a GE Signa 3T scanner (release VH3). FMRI series consisted of 36 contiguous oblique-axial sections acquired using a forward-reverse spiral sequence, which provides excellent fMRI sensitivity (Glover & Thomason, 2004). The image matrix was 64×64 over a 24 cm field of view for a $3.75 \times 3.75 \times 4$ mm voxel. The 36-slice volume was acquired serially at 1750 ms temporal resolution (TR) for 154 time points in each of five SLLT runs for a total of 770 time points. Anatomical images were also collected using 104–124 high-resolution Fast SPGR IR axial images [1, slice thickness; 1–1.5 mm, FOV (field of view); 24 cm, matrix size; 256×256] for each participant, used for co-registration and normalization purposes.

Statistical Analyses

To test Hypothesis one (performance), a series of repeated measures MANCOVAs were conducted (rmMANCOVAs). Because there are known sex (and age) differences in verbal memory, sex and age were used as covariates in all analyses. Where relevant, false positives were also used as covariates in order to account for performance variability potentially attributable to low engagement or inattention. A MANCOVA was also computed for CVLT-II long-delay free recall hits, as this is a frequently reported metric from the CVLT-II (Considine et al., 2011). MANCOVAs were computed for false positives from the CVLT-II (long-delay free recall, trial 1) and SLLT, covarying recall hits. Serial position curve effects were evaluated using rmMANCOVAs computed for SLLT and CVLT-II trial 1, with group as the independent variable (Cohen’s *d* also reported for comparison across tests and with existing literature) and recall in primacy (first four words), middle (six words in SLLT, eight words in CVLT-II), and recency phases (last four words).

To test hypothesis two (activation), fMRI data were processed and analyzed using MATLAB (The MathWorks, Natick, MA) with SPM8 and FSL (Friston et al., 1995). Slice timing, coregistration, and realignment were conducted at the individual subject level. Functional images were then normalized to fit a Montreal Neurological Institute (MNI) canonical template using DARTEL and were smoothed with a 5 mm FWHM kernel. The Encoding, Silent Rehearsal, Distraction, and Rest blocks were entered into first level models to determine global activation patterns for list learning, and contrast images were used in second level analyses (i.e., Encoding – Silent Rehearsal), with sex as a covariate. A second set of contrast images was also derived from behavioral data for memory hits to estimate the hemodynamic response function for the recall models in an event-related analysis (Words Recalled). Contrasts generated from Encoding – Silent Rehearsal and Words Recalled were analyzed to compare activation patterns between MDD and NDC.

Furthermore, as a follow-up, targeted test of hypothesis two, we utilized the MarsBaR toolbox (Brett, Anton, Valabregue, & Poline, 2002) to extract mean signal change during all blocks in regions of interest (ROIs) to evaluate Papez circuit specific ROIs in relationship to condition. These regions were based upon prior literature and a metaanalysis of explicit memory tasks (Kim, 2011, Schallmo et al., 2015). Mean activation in each region (10), by side (2), and by condition (4), was analyzed in a rmANOVA in SPSS. A total of ten spherical ROIs were created bilaterally in MarsBaR and mean signal was extracted for each of four conditions (Encoding, Distraction, Silent Rehearsal, Rest). Three spherical ROIs were created on the long axis of the hippocampus in twelve millimeter intervals, using MNI coordinates (30, -12, -18; 32, -24, -11; and 31, -36, -4). To determine ROI positions, we used activation foci from a recent meta-analysis (Kim, 2011) or those identified in two other independent studies of memory imaging (Beason-Held, Golski, Kraut, Esposito, & Resnick, 2005; Braskie, Small, & Bookheimer, 2009), and the Wake Forest PickAtlas (Maldjian, Laurienti, Burdette, & Kraft, 2003; Maldjian, Laurienti, & Burdette, 2004). A 5 mm radius spherical ROI was used for most regions except two that were smaller (mammillary bodies and fornix = 3 mm radius), and one that was larger (anterior insula = 7 mm radius). We note that the mammillary bodies are very close to air sinuses and may be less reliable. The fornix is primarily a white matter tract thus BOLD signal there may be less relevant to gray matter function and memory performance. All of these analyses used hits, false positives, sex and age as covariates.

To test Hypothesis three (activation to performance relationships), the mean ROI activation values were correlated with SLLT performance, separately in each group, to evaluate activation to performance relationships. Areas of significant effects (between group differences) were extracted from SPM maps using MarsBaR, consistent with our prior work (Langenecker et al., 2012). This strategy can help elucidate whether group differences are more specifically related to performance or disease group, or both. For the imaging analyses, two contrasts of primary interest were used: (1). Activation during the Encoding block minus the Silent Rehearsal block, and (2) Event-related analyses using the hemodynamic response function for Words Recalled were used for comparison as a second strategy to control for performance (only activation related to successfully recalled items are used, otherwise known as the subsequent memory effect, Kim, 2011).

AlphaSim correction (1000 Monte Carlo iterations) was used for all whole brain analyses, balancing height ($p < 0.005$) and extent (440 mm^3) thresholds to achieve a whole brain correction of $p < .05$. Behavioral performance and extracted ROI/Papez thresholds were set at $p < .05$ for theoretically based tests, uncorrected for multiple comparisons.

Results

Memory Performance Data

Hypothesis one predicted that MDD would display poorer memory performance for the CVLT-II and SLLT, compared to NDC. First, the hypothesis was tested for CVLT-II performance long-delay free recall, as that is typically reported in memory studies. There was no difference in performance between the groups for the CVLT-II long-delay free recall

hits [$F(1,60) = 1.41, p=.24, d=.25$, Figure 2A] or for CVLT-II long-delay free recall false positives, [$F(1, 60) = 0.64, p=.43$].

The second test of hypothesis one was for CVLT-II trial 1, in order to match to the subsequent SLLT analysis. In a rmANOVA testing group and group by serial position curve effects (3 serial positions: mean primacy, middle, recency values), NDC showed a trend toward greater recall hits on CVLT-II trial 1 compared to MDD [$F(1, 61) = 3.11, p=.08, d=.55$, Figure 2B]. The interaction of serial position curve with group was not significant [$F(2, 122) = 0.41, p=.67$]. There were no group differences in false positives for CVLT-II trial 1 [$F(1,61) = 0.01, p=.92$].

The third test of hypothesis one examined overall SLLT performance. During the SLLT, NDC exhibited greater recall overall [$F(1, 78) = 5.09, p=.03$]. The NDC and MDD groups did not differ on the number of false positives for the SLLT [$F(1, 78) = 0.91, p=.34$]. An additional, planned rmANOVA of 3 serial positions (mean primacy, middle, recency values) by 2 Group (MDD, NDC) revealed that NDC participants performed better than MDD participants [$F(1, 78) = 4.63, p=.04, d=.42$, Figure 2B]. The interaction of serial position curve with group was not significant [$F(2, 156) = 0.12, p=.89$].

Whole Brain Activation Differences Between Groups

Hypothesis two proposed that MDD would have decreased activation in frontoparietal and limbic regions relative to NDC. For comparison, the positive effect of Encoding-Silent Rehearsal condition for all participants, both NDC and MDD together, revealed activation in a broad fronto-temporal network (Supplemental Table 1, Figure 4A). The main contrast of interest was the Encoding block minus the Silent Rehearsal block, as our goal was to examine memory network(s) during the encoding phase as a foundation to establish memory circuitry differences in MDD compared to NDC. All of these analyses used hits, false positives, sex and age as covariates. NDC displayed greater activation than MDD in several regions including primarily bilateral middle frontal gyrus, dorsal anterior cingulate, insula, precuneus, superior parietal lobule, thalamus, and various cerebellar regions (Table 2, Figure 3A). MDD did not exhibit greater activation in any regions at the same threshold for the Encoding-Silent Rehearsal comparison. Z values of the following factors are also reported in Table 2, though, in this data, the majority of clusters were not affected by these factors: if individuals with MDD taking medications were excluded; effects based upon differences between MDD and MDD plus anxiety; ROI specific gray matter VBM differences.

Event Related (ER) analyses of Words Recalled were also conducted as a parallel analysis. For comparison, the positive effect of condition for all participants, both NDC and MDD in an overlapping analysis, revealed activation in fronto-temporal regions (Supplemental Table 1, Figure 4B). NDC displayed greater activation in the following gyri: primarily bilateral middle and inferior frontal, postcentral, parahippocampal, superior temporal, inferior occipital, anterior cingulate, and posterior cingulate cortices (Table 2, Figure 3B). NDC also exhibited greater activation in primarily bilateral precuneus, inferior parietal lobule, and claustrum (Table 2, Figure 3B). MDD did not exhibit greater activation in any regions for the ER analysis of Words Recalled.

Papez Circuit Specific ROI Activation Differences Between Groups

A rmANOVA was computed in SPSS including 10 Papez regions, 2 sides, 4 conditions, and 2 groups extracted using MarsBaR. Interactions between ROI and group [$F(9, 720) = 10.76$, $p < .01$], side, ROI, and group [$F(9, 720) = 2.31$, $p = .01$], and condition, ROI, and group [$F(27, 2160) = 1.89$, $p < .01$] were found. We focused on the interaction between condition, ROI, and group to test Hypothesis two, regarding condition and region-specific differences in MDD versus NDC. For purposes of illustration, we display activation for these regions in the two key conditions of interest (Encoding and Silent Rehearsal), and activation for the ER Words Recalled analysis (Figure 5). In the extracted activation averaged across hemispheres, MDD exhibited less activation than NDC during Encoding in the following regions: subgenual cingulate, mammillary bodies, posterior cingulate, and anterior, middle, and posterior hippocampi. MDD demonstrated less activation than NDC during Silent Rehearsal in the following regions: mammillary bodies, anterior insula, fornix, and anterior and middle hippocampi. The ER Words Recalled analysis revealed lower activation for MDD compared to NDC in nine of the ten Papez regions extracted: subgenual and rostral anterior cingulate, retrosplenial and posterior cingulate, mammillary bodies, anterior insula, fornix, and middle and posterior hippocampi (Figure 5).

Subsequent Memory Prediction in MDD

Hypothesis three investigated whether specific brain activation patterns were predictors of SLLT performance. Multiple regression models were conducted to establish a relationship between activation and performance in SPM8 using whole brain analyses, independently for each group. Multiple regressions of Encoding-Silent Rehearsal and recall hits revealed 13 fronto-temporal regions of greater activation related to better performance on the SLLT (Table 3). Greater activation for three (precentral, parahippocampal gyri and uncus) out of the 13 regions was related to enhanced recall on the SLLT in both NDC and MDD. Greater activation in the superior frontal and inferior frontal gyri as well as the insula and pulvinar of the thalamus were related to greater recall hits and lower false positives in NDC. In MDD, only greater activation in the lingual gyrus was related to lower false positives. For both NDC and MDD, greater activation in anterior cingulate was related to poorer performance (lower recall hits, Table 4).

Convergent and divergent validity for the SLLT and CVLT-II were evaluated with posthoc analyses assessing their relationships to each other and with different EF tasks (Supplemental Table 2). Five of 42 (11.9%) correlations of SLLT serial position curve measures with EF measures were significant, whereas nine of 42 (21.4%) correlations from CVLT-II serial position curve measures were significant.

Discussion

The present study found decreased memory performance and robustly decreased activation in fronto-limbic regions, including those that are key regions in the Papez circuit STM, and EF networks, in young and middle-aged adults with MDD, utilizing a task designed to specifically challenge memory pathways and diminish variability in how EF and STM may contribute to memory performance. Surprisingly, there were also decreases in somatosensory

areas in MDD. Within the Papez circuit, the mammillary bodies and middle hippocampi consistently displayed decreased activation in MDD in all three of the analysis conditions (Encoding, Silent Rehearsal, ER Words Recalled). When looking at all three conditions between groups, MDD showed decreased activation in many overlapping Papez regions across conditions, with each of the 10 Papez ROIs investigated showing decreased activation in MDD in at least one of the three conditions (Encoding, Silent Rehearsal, ER Words Recalled). Variability in performance explained activation differences between groups at a minimal level. Performance was a contributing factor for a substantial minority of regions - the majority of functional aberrations of memory networks in MDD are independent of performance variability. In contrast to the SLLT, there was no performance difference between groups on the CVLT-II long-delay free recall, one of the most widely used memory measures in neuropsychology practice (Camara, Nathan, & Puente, 2000; Rabin, Barr, & Burton, 2005).

The discrepancy between CVLT-II and SLLT performance results is interesting for a number of reasons. First, other studies report memory difficulties in MDD with the CVLT-II, typically for long-delay free recall, and effect sizes are moderate (Bora et al., 2013). The effect size for long-delay free recall for this study was small, suggesting that our sample may be a more conservative test of memory difficulties. As participants recruited for fMRI experiments must meet more stringent exclusion criteria (e.g., medical comorbidities, BMI, metal in the body), it is not surprising that the extent of memory difficulties observed would be less than in non-imaging studies. In older adult samples, these exclusion criteria might lead to a comparison of super-select MDD individuals without cognitive difficulties, especially due to worries about confounding depression- and dementia-related cognitive difficulties in older adults (Weisenbach et al., 2014a). Even in younger samples, exclusions related to tolerability, comorbidity, BMI, etc., could lead to a more restricted range of less ill MDD participants. Yet we still found differences between MDD and NDC in SLLT recall performance, suggesting that the SLLT is more sensitive to memory difficulties observed in MDD. Further, the present study investigates individuals with MDD ranging from only one episode to those with more chronic disease, possibly weakening the ability to show CVLT-II performance decrements in MDD; many other studies have reported that duration, severity, and chronicity of illness is related to memory difficulties in MDD (Snyder, 2013). Furthermore, the CVLT-II allows for multiple chances at encoding the same information, which can inform about the process of learning, but may underestimate real-world, one-trial learning realities often reported by individuals with MDD.

Our results reveal that both groups utilize similar networks during encoding of semantically-cued and grouped words, but NDC activate the networks to a greater extent. Some of these activation foci are related to performance in both groups, yet group differences remain when performance values are used as covariates, suggesting they are driven by disease or disease-by-network efficiency/utilization processes. It is notable, nonetheless, that for regions where performance to activation relationships are present, there is a challenge in interpreting whether these differences are due to overlap of performance and/or disease differences (e.g., see Miller, G. A., & Chapman, J. P., 2001 for discussion of challenges to covariation). These results suggest decreased utilization of distributed networks involved in memory for adults with MDD. We also note that frontal and parietal regions show decreased activation in

MDD, suggesting lesser involvement of STM and EF network(s) in semantically-cued explicit memory. It is possible that even when given an explicit strategy and cue as in the SLLT, MDD are less able to marshal EF resources to assist primary memory resources. It is also evident that implicit semantic cuing strategy (semantic clustering from CVLT-II) was related to SLLT performance in MDD and not NDC. Thus, semantic clustering, whether explicit or implicit, may play a larger role in individual differences in MDD than in NDC. Hence decreased activation in Papez circuit as well as STM and EF network regions co-occurs with decreased memory performance in some instances, reflecting decreased efficiency of these networks in the active disease state. In contrast, in some other regions, such as dorsal anterior cingulate, increased activation was associated with worse performance in MDD, suggesting that either conflict or mediation of interference might be reflected in activation within this region.

Follow-up studies to further parse the processes involved in deficient memory performance and strategies that can be employed to augment these weaknesses are needed. Investigating the specific strategies that individuals report when completing the SLLT may also prove useful. Memory performance declines with age in non-depressed individuals, and is negatively affected in individuals with MDD, therefore treatment for individuals with MDD might involve memory exercises to strengthen functioning and performance of memory network circuitry early on to ward off potential harmful effects of burden of illness. Effective and early treatment may stave off chronic burden and cognitive difficulties in mental illness (Weisenbach et al., 2014b).

Notably, previous work has shown a bias toward negative affect in MDD (Hsu, Langenecker, Kennedy, Zubietta, & Heitzeg, 2010), which may influence memory, possibly related to the amygdala activation observed in MDD during memory challenge (Ai et al., 2015; Roberson-Nay et al., 2006). Consideration of arousal and valence associated with words may be beneficial, as these can enhance memory processes (Bradley & Lang, 1999). In such studies it would be possible to test the negativity bias in memory and links to neural correlates by examining whether increased or decreased MDD memory performance is linked to decreased or increased activation in these regions, even with distraction paradigms.

Our study design does not allow disambiguation of several other factors that may be attributable to differences in memory performance. For example, state of illness effects are unconstrained, potentially distorting or combining trait and state symptoms. In addition, burden of illness or potential scarring effects of MDD over time are uncontrolled. Future research could examine memory and other cognitive domains across a longitudinal spectrum to elucidate burden of illness effects. Although we provided encoding strategy cues by presenting the semantic category of each list, we did not ask participants whether they employed other strategies for encoding. The significant correlations of SLLT values with semantic clustering, if only for MDD in primacy and middle phases of the serial position curve, suggest that those strategies were being used by some of the participants. Furthermore, although participants were matched on age in both groups, the large age range overall could have reduced the potential task effects observed, or masked age by disease interactions. Additionally, our sample was highly educated, which may impact performance and/or activation patterns. CVLT-II, other neuropsychological measures and the HDRS and

BDI were measured days to weeks before fMRI, potentially weakening relationships of these measures with SLLT and fMRI measures. Finally, our sample was not particularly ethnically diverse, and thus may not best represent the general population of individuals with MDD.

It remains imperative to pinpoint the underlying neural circuitry related to disrupted memory in MDD, such that effective targets for treatment and/or accommodation are pursued. As MDD is the largest disability cost in the 15–44 age range (World Health Organization, 2008), understanding and treating memory difficulties in addition to depressive symptoms is critical. Through refined neuroimaging techniques and with tasks like the SLLT, including a more ecologically valid presentation (e.g., single trial, with distraction), it may be possible to tease apart the neural network(s) dysfunction that contribute to impaired memory function in MDD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by funding from the National Institute of Mental Health (K-23 MH 074459, SAL), National Alliance for Research on Schizophrenia and Depression (SAL), the University of Michigan Depression Center (SAL, SLW), the University of Michigan fMRI Laboratory (SAL, SLW), and the University of Michigan Department of Psychiatry. We also thank Lawrence Own, Michael-Paul Schallmo, Kathleen E. Hazlett, Rachel E. Kay, Hadia Leon, Monique Bowles, Justin B. Miller, and Leslie Guidotti-Breting for their contributions to this project in data collection and processing. This work was presented in part at the 2013 Annual Meeting of Organization for Human Brain Mapping.

References

- Ai H, Opmeer EM, Veltman DJ, van der Wee NJA, van Buchem MA, Aleman A, van Tol MJ. Brain activation during emotional memory processing associated with subsequent course of depression. *Neuropsychopharmacology*. 2015; 40:2454–2463. [PubMed: 25857684]
- Ashendorf L, Constantinou M, McCaffrey RJ. The effect of depression and anxiety on the TOMM in community-dwelling older adults. *Archives of Clinical Neuropsychology*. 2004; 19(1):125–130. [PubMed: 14670385]
- Beason-Held LL, Golski S, Kraut MA, Esposito G, Resnick SM. Brain activation during encoding and recognition of verbal and figural information in older adults. *Neurobiology of Aging*. 2005; 26(2): 237–250. [PubMed: 15582751]
- Bora E, Harrison BJ, Davey CG, Yücel M, Pantelis C. Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder. *Psychological Medicine*. 2012; 42:671–681. [PubMed: 21910935]
- Bora E, Harrison BJ, Yücel M, Pantelis C. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychological Medicine*. 2013; 43:2017–2026. [PubMed: 23098294]
- Bradley, MN.; Lang, PJ. *Affective norms for English words (ANEW)*. Gainesville, FL: NIMH Center for the Study of Emotion and Attention; 1999.
- Braskie MN, Small GW, Bookheimer SY. Entorhinal cortex structural and functional MRI response during an associative verbal memory task. *Human Brain Mapping*. 2009; 30:3981–3992. [PubMed: 19507155]
- Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. *The American Journal of Psychiatry*. 2000; 157(1):115–117. [PubMed: 10618023]

- Bremner JD. Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. *The American Journal of Psychiatry*. 2004; 161(4): 637–645. [PubMed: 15056509]
- Brett M, Anton JL, Valabregue R, Poline JP. Region of interest analysis using an SPM toolbox. *NeuroImage*. 2002; 16:497.
- Brown JA. Some tests of the decay theory of immediate memory. *Quarterly Journal of Experimental Psychology*. 1958; 10:12–21.
- Camara WJ, Nathan JS, Puente AE. Psychological test usage: implications in professional psychology. *Professional Psychology: Research and Practice*. 2000; 31:141–154.
- Cole J, Costafreda SG, McGuffin P, Fu CHY. Hippocampal atrophy in first episode depression: A meta-analysis of magnetic resonance imaging studies. *Journal of Affective Disorders*. 2011; 134:483–487. [PubMed: 21745692]
- Considine CM, Weisenbach SL, Walker SJ, McFadden EM, Franti LM, Bieliauskas LA, ... Langenecker SA. Auditory memory decrements, without dissimulation, among patients with major depressive disorder. *Archives of Clinical Neuropsychology*. 2011; 26:445–453. [PubMed: 21593060]
- Delis, D.; Kramer, J.; Kaplan, E.; Ober, B. California Verbal Learning Test-II. San Antonio, TX: The Psychological Corporation; 2000.
- Dietsche B, Backes H, Stratmann M, Konrad C, Kircher T, Krug A. Altered neural function during episodic memory encoding and retrieval in major depression. *Human Brain Mapping*. 2014; 1–10.
- Elderkin-Thompson V, Moody T, Knowlton B, Hellemann G, Kumar A. Explicit and implicit memory in late-life depression. *The American Journal of Geriatric Psychiatry*. 2011; 19(4):364–373.
- First, MB.; Spitzer, RL.; Gibbon, M. Structured clinical interview for DSM-IV axis I disorder. New York: Biometrics Research Department, New York State Psychiatric Institute; 1995.
- Friston K, Ashburner J, Frith C, Poline JB, Heather J, Frackowiak R. Spatial registration and normalization of images. *Human Brain Mapping*. 1995; 2:165–189.
- Glover GH, Thomason ME. Improved combination of spiral-in/out images for BOLD fMRI. *Magnetic Resonance in Medicine*. 2004; 51(4):863–868. [PubMed: 15065263]
- Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry*. 1960; 23:56–62.
- Hermens DF, Naismith SL, Redoblado-Hodge MA, Scott EM, Hickie IB. Impaired verbal memory in young adults with unipolar and bipolar depression. *Early Intervention in Psychiatry*. 2010; 3:227–233. [PubMed: 20712728]
- Hsu DT, Langenecker SA, Kennedy SE, Zubieta JK, Heitzeg MM. FMRI BOLD responses to negative stimuli in the prefrontal cortex are dependent on levels of recent negative life stress in major depressive disorder. *Psychiatry Research: Neuroimaging*. 2010; 123(3):202–208. [PubMed: 20685091]
- Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, Frangou S, Williams SCR. Structural neuroimaging studies in major depressive disorder: Meta-analysis and comparison with bipolar disorder. *Archives of General Psychiatry*. 2011; 68(7):675–690. [PubMed: 21727252]
- Kim H. Neural activity that predicts subsequent memory and forgetting: A meta-analysis of 74 fMRI studies. *NeuroImage*. 2011; 54:2446–2461. [PubMed: 20869446]
- Langenecker SA, Caveney AF, Persad CP, Giordani B. Semantic List Learning Test. Ann Arbor. 2004
- Langenecker SA, Kennedy SE, Guidotti LM, Briceño EM, Own LS, Hooven T, ... Zubieta JK. Frontal and limbic activation during inhibitory control predicts treatment response in major depressive disorder. *Biological Psychiatry*. 2007a; 62:1272–1280. [PubMed: 17585888]
- Langenecker SA, Zubieta JK, Young EA, Akil H, Nielson KA. A task to manipulate attentional load, set-shifting, and inhibitory control: Convergent validity and test-retest reliability of the Parametric Go/No-Go Test. *Journal of Clinical and Experimental Neuropsychology*. 2007b; 29:842–853. [PubMed: 17852593]
- Langenecker, SA.; Lee, HJ.; Bieliauskas, LA. Neuropsychology of depression and related mood disorders. In: Grant, I.; Adams, K., editors. *Neuropsychological Assessment of Neuropsychiatric and Neuromedical Disorders*. UK: Oxford University Press; 2009. p. 532–559.

- Langenecker SA, Weisenbach SL, Giordani B, Briceño EM, Guidotti-Breting LM, Schallmo MP, ... Starkman MN. Chronic hypercortisolemia and affective dysfunction. *Neuropharmacology*. 2012; 62(1):217–225. [PubMed: 21787793]
- Lee AL, Ogle WO, Sapolsky RM. Stress and depression: Possible links to neuron death in the hippocampus. *Bipolar Disorders*. 2002; 4(2):117–128. [PubMed: 12071509]
- Liu X, Li L, Xiao J, Yang J, Jiang X. Abnormalities of autobiographical memory of patients with depressive disorders: A meta-analysis. *Psychology and Psychotherapy: Theory, Research and Practice*. 2013; 86(4):353–373.
- MacQueen GM, Yucel K, Taylor VH, Macdonald K, Joffe R. Posterior hippocampal volumes are associated with remission rates in patients with major depressive disorder. *Biological Psychiatry*. 2008; 64:880–883. [PubMed: 18722590]
- MacQueen G, Frodl T. The hippocampus in major depression: Evidence for the convergence of the bench and bedside in psychiatric research? *Molecular Psychiatry*. 2011; 16(3):252–264. [PubMed: 20661246]
- Maldjian JA, Laurienti PJ, Burdette JB, Kraft RA. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage*. 2003; 19:1233–1239. [PubMed: 12880848]
- Maldjian JA, Laurienti PJ, Burdette JB. Precentral gyrus discrepancy in electronic versions of the Talairach Atlas. *NeuroImage*. 2004; 21(1):450–455. [PubMed: 14741682]
- McEwen BS, Magariños AM, Reagan LP. Studies of hormone action in the hippocampal formation: Possible relevance to depression and diabetes. *Journal of Psychosomatic Research*. 2002; 53(3): 883–890. [PubMed: 12377298]
- Miller GA, Chapman JP. Misunderstanding analysis of covariance. *Journal of Abnormal Psychology*. 2001; 110(1):40–48. [PubMed: 11261398]
- Milne AMB, MacQueen GM, Hall GBC. Abnormal hippocampal activation in patients with extensive history of major depression: an fMRI study. *Journal of Psychiatry and Neuroscience*. 2012; 31(1): 28–36. [PubMed: 21745440]
- Mulligan NW. Implicit memory and depression: Preserved conceptual priming in subclinical depression. *Cognition and Emotion*. 2011; 25(4):730–739. [PubMed: 21547774]
- Papez JW. A proposed mechanism of emotion. *Archives of Neurology and Psychiatry*. 1937; 7:103–112.
- Peterson LR, Peterson MJ. Short-term retention of individual verbal items. *Journal of Experimental Psychology*. 1959; 58:193–198. [PubMed: 14432252]
- Rabin LA, Barr WB, Burton LA. Assessment practices of clinical neuropsychologists in the United States and Canada: A survey of INS, NAN, and APA Division 40 members. *Archives of Clinical Neuropsychology*. 2005; 20:33–65.
- Riggs E, Carr A, Bogue J, Dooley B. Reductions in specific first memories in depression: Influences of distraction, referential set and cue word valence on first memory retrieval. *The Irish Journal of Psychology*. 2005; 26(3–4):177–184.
- Roberson-Nay R, McClure EB, Monk CS, Nelson EE, Guyer AE, Fromm SJ, ... Pine DS. Increased amygdala activity during successful memory encoding in adolescent major depressive disorder: An fMRI study. *Biological Psychiatry*. 2006; 60(9):966–973. [PubMed: 16603133]
- Rogers MA, Kasai K, Koji M, Fukuda R, Iwanami A, Nakagome K, ... Kato N. Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neuroscience Research*. 2004; 50:1–11. [PubMed: 15288493]
- Sapolsky RM. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. *Biological Psychiatry*. 2000; 48(8):755–765. [PubMed: 11063972]
- Schallmo MP, Kassel MT, Weisenbach SL, Walker SJ, Guidotti-Breting LM, Rao JA, Hazlett KE, Considine CM, Sethi G, Vats N, Pecina M, Welsh RC, Starkman MN, Giordani B, Langenecker SA. A New Semantic List Learning Task to Parse the Functioning of the Papez Circuit. *Journal of Clinical and Experimental Neuropsychology*. 2015; 37(8):816–833. [PubMed: 26313512]
- Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. *American Journal of Psychiatry*. 2003; 160(8):1516–1518. [PubMed: 12900317]

- Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychological Review*. 1992; 99:195–231. [PubMed: 1594723]
- Watkins E, Brown RG. Rumination and executive function in depression: an experimental study. *Journal of Neurology, Neurosurgery & Psychiatry*. 2002; 72:400–402.
- Weisenbach SL, Kassel MT, Rao JA, Weldon AL, Avery ET, Briceño EM, ... Langenecker SA. Differential prefrontal and subcortical circuitry engagement during encoding of semantically related words in patients with late life depression. *International Journal of Geriatric Psychiatry*. 2014a10.1002/gps.4165
- Weisenbach SL, Marshall DF, Weldon AL, Ryan KA, Vederman AC, Kamali M, ... Langenecker SA. The double burden of age and disease on cognition and quality of life in bipolar disorder. *International Journal of Geriatric Psychiatry*. 2014b; 29(9):952–961. [PubMed: 24677268]
- Werner NS, Meindl T, Materne J, Engel RR, Huber D, Riedel M, ... Hennig-Fast K. Functional MRI study of memory-related brain regions in patients with depressive disorder. *Journal of Affective Disorders*. 2009; 119:124–131. [PubMed: 19346000]
- World Health Organization. The Global Burden of Disease: 2004 Update. WHO; 2008.

Figure 1.

Diagram of Semantic List Learning Test. Participants are presented with 15 lists of 14 semantically related words (210 words total). Each list is preceded by its semantic category cue. A period of instructed silent rehearsal follows a distractor task after each list in the fMRI scanner, whereas free recall is conducted upon completion of the scanning session, outside of the scanner.

Figure 2.

(**A**) Percent recall of the CVLT-II long-delay free recall (CVLT-LDFR) by Group; (**B**) Percent recall along the Serial Position Curve by Task (CVLT-II Trial 1, SLLT mean performance) and by Group. (NDC = Never-Depressed Comparisons; MDD = Major Depressive Disorder).

Figure 3. Brain regions of significantly greater activation for Never-Depressed Comparisons than Major Depressive Disorder during the (A) Encoding minus Silent Rehearsal condition and the (B) Event Related Words Recalled condition.

Figure 4. Brain regions of significant greater activation in the **(A)** Encoding minus Silent Rehearsal condition and the **(B)** Event Related Words Recalled condition for both groups (NDC and MDD).

Figure 5.

Illustrates the significant interaction between condition, regions of interest (ROI), and group. Displays activation for 10 Papez ROIs in the two key conditions of interest (Encoding and Silent Rehearsal), as well as activation for the Event Related Words Recalled analysis.

Table 1

	NDC		MDD	
	<i>n</i> = 40		<i>n</i> = 42	
Variables	<i>M</i> (<i>SD</i>)	<i>Range</i>	<i>M</i> (<i>SD</i>)	<i>Range</i>
Gender (<i>n</i> female)	19	--	23	--
Age (years)	37.7 (17.3)	18–65	43.3 (16.7)	20–65
Education (years)	15.8 (1.8)	13–19	16.0 (2.1)	12–21
Estimated Verbal IQ ^{<i>I</i>}	113.7 (9.5)	80–129	113.0 (8.6)	91–125
Hamilton Depression Rating Scale [*]	0.7 (1.1)	0–5	15.1 (6.4)	4–33
Beck Depression Inventory [*]	1.7 (3.5)	0–18	22.5 (11.0)	4–48
On psychotropic medication (%)	N/A	--	40.5%	--

Note.

^{*I*} Estimated from the Shipley-2, Verbal subtest, administered in Superlab 2.

^{*} *p* < .05.

NDC = Never-Depressed Comparison; MDD = Major Depressive Disorder.

Supplemental Table 3 compares MDD with and without medications. Those taking medications are significantly older than those not taking medications.

Table 2
Brain regions of significantly greater activation for NDC relative to MDD during the SLLT

Contrast/lobe	Talairach coordinates					
	BA	x	y	z	mm ³	Z
Blk, Encoding minus Silent Rehearsal						
Frontal						
Middle Frontal ^{#A}	6	26	-7	54	592	3.79
Parietal						
Precuneus	7	10	-56	41	2072	3.48
	19	-32	-62	39	1272	3.4
Superior Parietal Lobule	7	12	-60	55	1728	3.5
Insula	13	-38	26	15	392	3.61
	13	34	14	-7	272	3.07
Dorsal Anterior Cingulate	32	-8	18	36	792	3.42
Subcortical						
Cerebellum, Cerebellar Tonsil	26	-62	-33	-33	1312	3.92
	-38	-62	-33	-33	512	3.35
Cerebellum, Culmen of Vermis	45	-48	-20	-20	664	3.35
Cerebellum, Dentate Nucleus	-15	-58	-21	-21	312	3.14
Clastrum	-24	16	-8	-8	904	3.39
Thalamus	13	-9	17	17	648	3.78
ER, Words Recalled						
Frontal						
Anterior Cingulate [#]	24	-6	16	25	2992	3.98
	24	4	23	17	2160	3.53
Inferior Frontal	13	-27	14	-10	1544	3.6
Middle Frontal [#]	6	26	-7	43	1336	3.83
	6	24	18	48	816	3.62
Parietal						
Precuneus	7	-8	-65	42	13200	4.18

Contrast/lobe	Talairach coordinates					
	BA	x	y	z	mm ³	Z*
Postcentral [#]	19	-29	-60	42	2072	3.63 2.81
Posterior Cingulate	3	-24	-34	56	2656	3.97 2.25
Inferior Parietal Lobule	31	17	-60	14	1088	4.31 2.39
	40	43	-38	45	448	3.84 2.07
Temporal	39	33	-58	39	320	3.07 1.74
Parahippocampal	34	-17	-7	-16	528	3.49 2.81
Superior Temporal ^{##}	22	-48	-15	-6	392	3.28 1.98
Occipital						
Inferior Occipital	19	-36	-75	-6	536	3.97 2.5
Subcortical						
Clastrum		-38	-21	-3	344	3.17 2.16

Note. No areas of greater activation for MDD were found in the above contrasts. Blk = Block Design, ER = Event-related

* Z value when excluding medicated MDD participants (i.e. NDC greater than unmedicated MDD). Note the medicated MDD participants typically have greater severity on many illness metrics, also observed in this sample. Note all results remain in the same direction if equivalent or diminished extent.

[#] Regions where a significant grey matter volumetric subcluster difference was found between groups (NDC > MDD)

[^] region where a subcluster of reduced gray matter volume was inversely correlated with activation in the MDD group ($r = -.32$, $p = .04$).

[#] region where a subcluster of reduced gray matter volume was positively correlated with activation in the MDD group ($r = .31$, $p = .05$).

Table 3

Whole brain activation correlated with better SLT performance for Encoding minus Silent Rehearsal, by Group.

Contrast/lobe	Talairach coordinates				
	BA	x	y	z	mm ³
Blk, Activation Associated with Higher Recall Hits					
Never-Depressed Comparisons					
Frontal					
Precentral	4	26	-17	46	5784 5.3
Superior Frontal	8	-13	30	47	2640 3.88
Subgenual Cingulate	25	1	10	-2	1528 4.42
Middle Frontal	11	24	32	-13	1248 3.85
Insula	13	40	-5	5	504 3.08
Medial Frontal	9	-11	37	32	328 4.01
Inferior Frontal	47	-25	34	-7	352 3.2
Rectal	11	-8	30	-18	272 3.35
Temporal					
Uncus	28	24	1	-25	9104 5.24
Middle Temporal	39	-45	-67	16	992 3.49
Insula	13	50	-34	17	808 3.27
Parahippocampal	30	15	-40	-1	368 3.56
Occipital					
Inferior Occipital	19	-38	-69	-6	12520 5.86
Fusiform	18	27	-93	-10	13136 5.75
Subcortical					
Thalamus, Pulvinar	8	-36	12	264	3.37
Major Depressive Disorder					
Frontal					
Precentral	4	-31	-23	58	744 3.92
Dorsal Cingulate	24	-10	-11	40	560 3.71
Parietal					
Postcentral	2	-36	-27	42	2936 4.97

Contrast/lobe	Talairach coordinates				Z
	BA	x	y	z	
Temporal					
Uncus	28	-27	-11	-27	7704 4.11
Superior Temporal	38	27	6	-32	5296 4.38
	41	-41	-29	14	1064 3.9
Parahippocampal	28	22	-17	-17	1224 3.87
	36	-25	-34	-14	272 3.54
Inferior Temporal	20	-59	-17	-21	800 4
	20	59	-17	-21	704 4.11
Occipital					
Inferior Occipital	18	-25	-89	-10	10632 5.59
Fusiform	18	24	-98	-14	7560 5.64
Blk, Activation Associated with Lower False Positives					
Never-Depressed Comparisons					
Frontal					
Inferior Frontal	13	31	10	-9	2792 3.4
	47	-38	28	-8	472 3.29
Superior Frontal	8	-24	14	43	728 4.08
Dorsal Anterior Cingulate	24	-13	4	44	504 3.63
Insula	13	-32	12	11	376 3.21
Parietal					
Precuneus	7	19	-73	40	376 3.51
Posterior Cingulate	23	12	-38	21	2296 3.78
	23	-6	-34	23	728 4.03
Occipital					
Precuneus	31	-15	-62	19	1752 3.87
	31	12	-62	21	320 3.39
Subcortical					
Cerebellum, Nodule of Vermis		-3	-56	-24	2528 3.82
Cerebellum, Dentate Nucleus		-18	-56	-19	520 3.39
Cerebellum, Culmen of Vermis		33	-52	-14	264 3.35

Contrast/lobe	BA	Talairach coordinates				mm ³	Z
		x	y	z			
Thalamus, Ventral Lateral Nucleus		-11	-11	4		1288	3.51
Thalamus, Medial Dorsal Nucleus		4	-13	15		456	3.69
Thalamus, Pulvinar		-10	-29	19		440	3.85
		-4	-27	2		336	3.46
Thalamus		13	-15	6		320	3.47
Putamen, Lentiform Nucleus		-27	4	-4		448	3.03
Major Depressive Disorder							
Occipital							
Lingual	18	19	-75	6		304	3.42

Note. Blk = Block Design, ER = Event-related

Whole brain activation correlated with poorer SLT performance for Encoding minus Silent Rehearsal, by Group.

Table 4

Contrast/lobe	Talairach coordinates					
	BA	x	y	z	mm ³	Z
Blk, Activation Associated with Lower Recall Hits						
Never-Depressed Comparisons						
Frontal						
Anterior Cingulate	32	6	16	36	6352	5.69
	32	-4	24	33	3272	5.09
Precentral	6	-34	3	30	2968	3.99
Middle Frontal	10	-31	51	4	1712	4.01
	46	41	26	22	992	4.07
	6	31	4	49	272	3.28
Parietal						
Posterior Cingulate	23	-1	-34	21	448	4.2
Occipital						
Lingual	18	6	-81	-8	112592	7.65
Subcortical						
Clastrum		-29	20	-1	1288	3.56
		29	18	1	1264	4.46
Major Depressive Disorder						
Frontal						
Anterior Cingulate	32	-8	12	37	62664	6.07
Superior Frontal	10	19	51	-3	1576	4.56
	10	-25	43	5	536	3.68
Temporal						
Parahippocampal	30	-17	-34	-2	10968	4.77
	19	40	-38	1	384	3.58
Superior Temporal	22	48	-25	-7	4000	3.98
	38	45	14	-14	328	4.03
Middle Temporal	20	-52	-36	-7	2488	3.84

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Contrast/lobe	Talairach coordinates					mm ³	Z
	BA	x	y	z			
Inferior Temporal	37	-45	-44	-18		664	3.39
Occipital							
Lingual	18	-4	-83	-12		171040	6.96
Subcortical							
Clastrum		29	20	-1		5584	5.21

Note. No areas of greater activation significantly associated with high false positives were found for either NDC or MDD groups. Blk = Block Design