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Differential Resting State Connectivity Patterns and Impaired Semantically Cued List Learning Test Performance in Early Course Remitted MDD

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Abstract

Objective—There is a well-known association between memory impairment and Major Depressive Disorder (MDD). Additionally, recent studies are also showing resting-state (rs) fMRI abnormalities in active and remitted MDD. However, no studies to date have examined both resting state connectivity and memory performance in early course remitted MDD, nor the relationship between connectivity and semantically-cued episodic memory.

Method—Resting state MRI (rsMRI) data from two 3.0 Tesla GE scanners were collected from 34 unmedicated young adults with remitted MDD (rMDD) and 23 healthy controls (HCs) between 18–23 years of age using bilateral seeds in the hippocampus. Participants also completed a semantically-cued list-learning test and their performance was correlated with hippocampal seed-based rsMRI. Regression models were also used to predict connectivity patterns from memory performance.

Results—After correcting for sex, rMDD performed worse than HCs on the total number of words recalled and recognized. rMDD demonstrated significant in-network hypoactivation between the hippocampus and multiple fronto-temporal regions, and multiple extra-network hyperconnectivities between the hippocampus and fronto-parietal regions when compared to HCs. Memory performance negatively predicted connectivity in HCs and positively predicted connectivity in rMDD.

Conclusions—Even when individuals with a history of MDD are no longer displaying active depressive symptoms, they continue to demonstrate worse memory performance, disruptions in hippocampal connectivity, and a differential relationship between episodic memory and hippocampal connectivity.

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Keywords

resting-state; remitted MDD; episodic memory; functional connectivity; fMRI; hippocampus

Introduction

Mounting evidence suggests the presence of state-related abnormalities in resting state connectivity in active MDD, particularly within subsystems of the default-mode network (Anand et al., 2005; Connolly et al., 2013; Frodl et al., 2010; Grecius et al., 2007; Jacobs et al., 2014; Liu et al., 2011; Sheline, Price, Yan, & Mintun, 2010). To a large extent, this work has focused on emotion-related phenomena, such as negative memory biases, sadness mood inductions, and rumination (Connolly et al., 2013; Hamilton, Chen, Thomason, Schwartz, & Gottlib, 2011; Jacobs et al., 2014). More recently, differential resting state patterns have also been observed in the remitted Major Depressive Disorder (MDD) state; specifically, hyperconnectivity from the default mode and salience networks to the cognitive control network (Jacobs et al., 2014). Even more intriguing, these differential patterns in MDD appear to be quite robust even early in the course of illness, and are related to persisting dysfunction, both in rumination and cognitive control (Connolly et al., 2013; Jacobs et al., 2014; Zhang et al., 2011). Other patterns of increased connectivity in early state illness appear to potentially offer some degree of resilience; such as in Zhang and colleagues (2011), who reported a negative correlation between left hippocampal connectivity and disease duration and severity in first-episode, medication-naïve MDD patients. Investigating and observing resting state connectivity patterns, especially as they relate to dysfunctional behaviors, performance, and affective responses collected at separate time points, increase confidence in the stability of the connectivity patterns and the relationships observed.

To date, these patterns of abnormal connectivity in both acute and remitted MDD have not yet been investigated in relation to one of the most common abnormalities observed in acute and chronic MDD—memory difficulties. Indeed, memory difficulties are extensively studied in MDD (see Burt, Zembar, Niederehe, 1995 for review); however, attention and executive functioning are more frequently examined in remitted MDD, as young adults in remission report these deficits to be the most prominent (Hasselbalch, Knor, & Kessing, 2011, Paelecke-Habermann, Pohl, & Leplow, 2005, Peters et al., 2015, Weiland-Fiedler et al., 2004). A review of remitted MDD literature examining memory, specifically, has demonstrated that remitted MDD individuals show deficits in nonverbal memory, largely due to difficulties organizing visual information (Behnken, et al., 2010), and middle-aged recovered and medicated melancholic patients display declines in delayed logical and visual memory (Marcos, et al., 1994),

The association between memory and MDD remains controversial, despite thousands of articles and several meta-analyses showing memory difficulties (e.g., Bora, Harrison, Yücel, & Pantelis, 2013; Considine, et al., 2011; Elderkin-Thompson, Moody, Knowlton, Hellemann, & Kumar, 2011; Hermens, Naismith, Redoblado-Hodge, Scott, & Hickie, 2010; Liu, Li, Xiao, Yang, & Jiang, 2013; Mulligan, 2011). In part, this controversy relates to whether the observed memory difficulties persist outside of active episodes (Snyder, 2013),

whether they predate and comprise a risk factor for depression (Porter, Gallagher, Thompson, & Young, 2003), whether they are a consequence of slowed information processing (Butters et al., 2004), or whether they are an epiphenomenon related to poor effort (Considine et al., 2011; Rohling, Green, Allen, & Iverson, 2002), easy distractibility, or ascertainment biases in the patients who actually arrive for studies and evaluations (e.g., those with MDD and no overt cognitive difficulties may never show up for studies, disability claims, or neuropsychological evaluations).

Studies of memory functioning in MDD have been further hampered by the use of tools that do not always distinguish between specific aspects of memory or less severe memory impairment (Burt, et al., 1995). List learning tasks with multiple learning trials allow for a dissociation of amnestic impairments from less severe difficulties with attention, distraction, encoding, and recognition, suitable for dementia and sever brain injury evaluations. Memory difficulties in MDD may still lead to disruptions in work, family and social functioning, if relatively less severe. Furthermore, a great majority of memory demands in real life involve one trial learning in distracting contexts. We designed an episodic memory task, the List Learning Test (SLLT) to engage one-trial learning and for use with fMRI (Langenecker, Caveney, Persad, & Giordani, 2004). The SLLT includes a distraction condition and targeted learning strategies (semantic cues) to reduce individual variance that might be attributed to short-term memory or memory organization strategies. To this end, we observed memory difficulties in adults with active MDD relative to age-matched controls (Kassel et al., under review), and equivalent memory performance when comparing depressed elders with older healthy controls (Weisenbach et al., 2014). Despite differences in memory performance on the SLLT between these two MDD age cohorts, both studies observed decreased temporal and frontal activation in active MDD, with the exception of increased left inferior frontal gyrus activation in elders with MDD. Inferior frontal activation was greater in elders with MDD relative to healthy controls, but this pattern was not observed in adults with MDD. These studies form an important nexus for understanding the nature, extent, and nuances in the neural bases of memory difficulties in MDD. However, a couple of limitations exist. First, the majority of these studies have used a wide age range, and it is not clear if there may be changes in memory performance in MDD that might be easier to observe earlier in the course of illness, before age associated memory decline occurs. Furthermore, study of active MDD may obscure persisting stable memory difficulties, or could even result in greater noise in measurement at the behavioral and neural circuit levels.

A final challenge to studies of this type is concern about the nature of activation differences when performance is not equivalent between groups. In this instance it is difficult to fully attribute any network or region differences in activation solely to the disease, as it may be driven by performance differences. In our work, we highlight how specific performance differences should be present, such that the disease process is reflected in a performance difference *and* the underlying network abnormalities that drive performance (Briceño et al., 2013; Kassel et al., under review; Langenecker et al., 2004; Langenecker et al., 2012). However, the challenge of parsimony remains - are these differences related to disease, performance, or disease and performance?

To address some of the existing weaknesses within the literature, some highlighted further by our own recent work, we undertook an investigation of memory performance in remitted MDD, using the SLLT while in the scanner. But in this case we did not use the activation-derived data during this task, only the performance-derived data. We hypothesized that resting state connectivity differences, using the hippocampus as a seed, would be present in remitted MDD, and these abnormalities would be related to both aspects of disease and memory performance. Through use of resting state connectivity, we can directly address the performance and network activation patterns separately, and then determine the degree to which they are related. Furthermore, to control for variance in age, as well as duration, severity and number of episodes of illness, we elected to conduct the most conservative test of the hypothesis of memory difficulties in MDD that we could determine. Namely, we restricted the study to only remitted MDD adults who were not taking any psychotropic medications and studied young adults to restrict developmental variance. We also carefully considered the role of sex on performance, given that known differences exist (i.e. females display enhanced verbal memory) in verbal memory performance (Kramer, Yaffe, Lengenfelder, & Delis, 2003; Lewin, Wolgers, & Herlitz, 2001).

Methods

Participants

The current study was approved by the University of Michigan (UM) and the University of Illinois at Chicago (UIC) Institutional Review Boards and all participants provided written informed consent. Recruitment for participation was conducted in Ann Arbor, MI and Chicago, IL and involved community flyers and Internet advertisements. All participants who met criteria via phone screen were invited for a baseline diagnostic interview, neuropsychological testing, and fMRI. Remitted MDD criteria include a history of at least one major depressive episode and a score less than 7 on the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960). The Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) was administered before neuropsychological testing and the day of scanning to confirm remitted status. Diagnosis of MDD history, as well as mean age of depression onset, number of depressive episodes, and a history of psychiatric hospitalization, was determined with the Diagnostic Interview for Genetic Studies (DIGS), and remitted MDD (rMDD) participants were required to be medication free for 30 days prior to their fMRI scan. Healthy control (HC) exclusion criteria included a history of MDD or any other Axis I or II psychiatric disorder, or a first-degree relative with a history of psychiatric illness. Participants in either group with a history of substance abuse or dependence within the previous six months were also excluded. The final sample included 34 rMDDs (17 UM, 17 UIC) and 23 HCs (14 UM, 9 UIC) participants ranging in age from18 to 23 years old. There were no significant differences between groups in age, sex, education, or estimated verbal IQ. The two groups did statistically differ in their HDRS scores. Residual symptoms may be in part related to any effects observed. Notably, though, a two-point mean difference in HDRS at this low of a score is not clinically meaningful. See Table 1 for demographic and clinical information.

The Semantic List Learning Test (SLLT) and the Neuropsychological Battery

This Semantic List Learning Test has been previously described by Weisenbach and colleagues (2014) and Langenecker et al. (2004). In brief, the SLLT is a learning and memory task composed of three blocks—encoding, distraction, and silent rehearsal— with 12 lists completed over four different scanning runs (3 lists per run). There is an additional recall and recognition phase conducted immediately post-scan, outside of the scanner. During encoding, participants were presented with a semantically-related word list (e.g. tools, vegetables, etc.) containing 14 words. Participants were prompted with the name of the semantic category for 3.5 seconds at the start and then words were presented one at a time for one second each with a one to four second jittered inter-stimulus interval. They were instructed to read each word silently to themselves without moving their lips and to try to remember each word, using the semantic cue to aid in encoding and in recall phases. During the interval, a fixation cross was displayed and each encoding block lasted 58.25 seconds. Following each encoding block, participants completed the distractor task for 14 seconds, which involved pressing a key every time an x, y, or z was presented in a serial stream of letters. This distractor block was included to prevent recency effects during delayed recall/recognition by inhibiting rehearsal of items in short-term memory (Brown, 1958, Peterson & Peterson, 1959, Schallmo, et al., 2015). This distraction prevents initial consolidation, which then carries over to any later recall or recognition prompts.. All participants received the same word lists, though the presentation of the words within a list and the order of the three lists within each run were randomized. At the end of each of the four runs there was a 32-second rest period. Immediately following the scan, participants were given sheets of paper with all of the category cues and told to write down all the words they could recall from each semantic category (delayed recall). Finally, they were given a written list of all of the previously presented words (168 words in all) and 210 foil words, and told to circle those words they had seen before (recognition). Performance dependent variables for all analyses were number of cued recalled words minus false positive recalled words, and number of recognized words minus recognition false positive words. D′ was also calculated for recall and recognition.

The neuropsychological battery consisted of the Shipley-2 Verbal subtest (Shipley, Gruber, Martin, & Klein, 2009), California Verbal Learning Test-2nd edition (Delis, Kramer, Kaplan, & Ober, 2000) semantic and phonemic fluency, Benton Visual Form Discrimination (Benton, Hamsher, Varney, & Spreen, 1978), Purdue Pegboard (Lezak, 1995), Digit Symbol Coding (Wechsler, 2008), Trail Making Test (Reitan, 1992, Stroop Color/Word Test (Stroop, 1938), and the Wisconsin Card Sorting Test (Grant & Berg, 1948).

fcMRI Acquisition

The resting state scan was acquired following the administration of the SLLT. MR data were acquired at two imaging sites: UM and UIC. Scans taking place at UM involved an eyes-open resting state scan acquired over eight minutes on a 3.0 T GE Signa scanner using a T2* weighted single shot reverse spiral sequence (29 4-mm thick slices, TE = 30 ms; TR = 2000 ms; flip angle = 90°; FOV = 20; matrix = 64 x 64). Eyes-open resting scans at UIC were also acquired over eight minutes on a 3.0 T GE Discovery scanner using parallel imaging with ASSET and T2* gradient-echo axial echo planar imaging sequence (44 3-mm thick slices,

TE = 22.2 ms; TR = 2000 ms; flip angle = 90°; FOV = 22; matrix = 64 x 64). At both sites, participants were told to focus on a fixation cross, and high-resolution T1 anatomic scans were obtained for spatial normalization. Due to potential artifacts of using two different scanners with different acquisition parameters, we previously examined between-site differences in resting state connectivity and found that the influence of site on fMRI findings was minimal (see Jacobs, et. al, 2014 for details).

fcMRI Preprocessing

Slice timing was completed with SPM8 and motion detection algorithms were applied using FSL. After realignment, volumes with movement or artifacts greater than 1.5mm over three volumes or less were interpolated. Only one subject required interpolation. Then, frame to frame (FTF) values in pitch, roll, and yaw deviations (as well as SDs of these mcflirt adjustments in FSL) were examined and compared between groups (ns, ps < .31). Five HCs and 2 rMDDs had more than 1 FTF movement exceeding .5 mm, although the mean FTF for both groups was less than 1. Analyses were conducted with and without these seven individuals, with no notable differences in results. As such, these seven individuals were included in all analyses. Those excluded to excessive movement in our prior report were not included for any part of this experiment (Jacobs et al., 2014). Of note, mean of standard deviation in pitch was significantly correlated with FTF values exceeding .5 ($r = .52$, $p < .05$). Structural images were co-registered to functional images and then the co-registered T1-SPGR underwent spatial normalization to the Montreal Neurological Institute (MNI) template. The resulting normalization matrix was then applied to the slice-time-corrected, movement corrected, time series data and smoothed with a 5 mm Gaussian kernel. Resulting T2* images were 2 mm on a side with isotropic voxels.

Cross-Correlation Analysis

The seeds of interest were the left and right anterior hippocampus, using the following coordinates: −30 −12 −18 and 30 −12 −18, respectively. These two spherical ROIs (2.9 mm radius, 19 voxels) were created in the MarsBaR toolbox (Brett, Anton, Valabregue, & Poline, 2002) and were defined in MNI space. These coordinates were confirmed on the MNI brain visually, as well as upon an average T_1 brain of all subjects, and were visually confirmed to have minimal overlap with the amygdala on the average brain. Spatially averaged time course data were extracted from these ROIs for each participant. Correlation coefficients between mean time course for the two seed regions and all other voxels of the brain were calculated, resulting in a 3-dimensional correlation coefficient image (r image). These r images were transformed to z-scores using a Fisher transformation and were used in independent samples *t* tests conducted in SPM8. AlphaSim correction (1000 iterations) was used for analysis, balancing height ($p < .005$) and extent (440 mm^3) thresholds to achieve a whole brain correction of $p < .05$. All analyses included use of sex as a covariate.

In-network masks were derived from the HC correlational image for both seeds and were applied to each contrast (HC > rMDD, in network; HC < rMDD, out of network) to determine in-network vs. out-of-network activation regions for each seed. Importantly, there are functional implications about whether group differences might be observed in memory supportive regions/networks, or “in-network”, or in other, potentially extraneous regions that

may or may not be supportive of memory performance, or "out of network." MarsBaR was used to extract mean z values from each cluster of significant differences between groups separately for each seed and person. These values were then correlated with SLLT delayed recall and recognition performance for each group and the Hamilton Depression Rating Scale (rMDD only). Regression analysis was also used to examine the relationship between connectivity in both groups using both the left and right hippocampal seeds and SLLT cued recall and recognition performance. Due to the limitations of the SPM software, the direction of the analyses used SLLT memory performance to predict hippocampal connectivity; however, the nature of the correlation remains the same within a cross-sectional study like this. It is assumed that connectivity is in fact predicting performance.

Results

Behavioral Analysis of SLLT and Neuropsychological Performance

When examining both delayed recall and recognition performance on the SLLT, the scores were calculated by subtracting the number of false positives from the number of correct target hits. In doing so, the two groups significantly differed in their performance, with the HC group demonstrating a greater number of targets recalled ($F(1, 55) = 5.6$, $p = 0.021$, $d = 0.65$) and recognized ($F(1, 55) = 6.0$, $p = 0.018$, $d = 0.67$). However, when calculating the sensitivity index for both SLLT delayed cued recall and recognition, d′ was not significantly different between groups. When comparing the HC and rMDD groups on performance while controlling for sex, the diagnostic groups statistically differed in the total number of both recall [$F(1, 55) = 24.5$, $p < 0.001$, $d = 0.73$] and recognition [$F(1,55) = 53.4$, $p < 0.001$, $d = 0.73$], with the HC group having better delayed recall and recognition scores. Similarly, d′ was significantly different between groups for both SLLT delayed cued recall [$F(1,54) = 4.59$, $p = 0.037$, $d = 0.58$] and recognition [$F(1,54) = 5.33$, $p = 0.025$, $d = 0.63$] while controlling for sex.

There were no significant sex differences in SLLT delayed recall [$F(1, 54) = 0.037$, $p = 0.849$, HC: $d = 0.4$, rMDD: $d = 0.4$] or recognition [$F(1, 54) = 0.002$, $p = 0.966$, HC: $d = 0.3$, rMDD: $d = 0.3$) performance, covarying for group, see Table 2. The HC and the rMDD groups did not statistically differ in proportion of individuals by sex, however, there was still an imbalance of males (fewer) and females in both the rMDD and HC groups, as seen in Table 1. Therefore, these behavioral data were transformed into sex-corrected z-scores, using separate male and female means and standard deviations. The following results all used these sex-corrected z-scores when assessing SLLT performance predicting connectivity differences between groups. There were no significant differences in performance between groups on all neuropsychological tests, see Table 2. We also present the serial position curve values for each group and each sex in Figure 4.

Within Network fMRI Connectivity: Differences between Groups and Relationship to Memory

The network was derived from the HC pattern of connectivity for both the left and right hippocampal seeds, to highlight those regions that should be most directly related to memory performance. Within the network, there were no areas that demonstrated increased

connectivity in the rMDD group compared to HC. However, there were numerous areas of increased within-network connectivity in the HC group versus the rMDD group (see Figures 1 and 2). The HC group demonstrated significantly greater connectivity between the left hippocampus and the right superior frontal region compared to rMDD. Additionally, there was greater connectivity between the right hippocampus and the left middle and superior frontal regions, the left inferior temporal region, the left insula, and the right posterior cingulate in the HC group compared to rMDD. Only one of these differential regions (HC > rMDD) was significantly related to SLLT performance. Specifically, in only the HC group, the connectivity between the right hippocampus and the left superior frontal region was positively correlated with both SLLT delayed recall (r = 0.46, p = 0.029) and recognition performance (r = 0.48, p = 0.02). See Table 3.

Extra-Network fMRI Connectivity: Differences between Groups and Relationship to Memory

Likely due to using HC connectivity as the network mask, there were no regions outside the network that demonstrated greater connectivity in the HC group than in rMDD. Extra, or out of network areas are not as strongly hypothesized to support memory processes. There were multiple extra-network ROIs demonstrating significantly greater connectivity to the left and right hippocampal seeds in the rMDD group (reported in Table 4, seen in Figures 1 and 2). Specifically, the left hippocampus exhibited greater connectivity to bilateral anterior cingulate, left paracentral lobule, middle frontal, and superior temporal regions, as well as to the right medial frontal, posterior cingulate, and supramarginal regions. When correlating the strength of connectivity between these left hippocampal connections (rMDD > HC) and SLLT performance and the HDRS, the rMDD group demonstrated a positive relationship with the right anterior cingulate and both SLLT delayed recall and recognition (r = 0.35, p = 0.041 and r = 0.36, p = 0.035, respectively). There was also a positive correlation between left hippocampus to right supramarginal connectivity with SLLT recognition performance (r = 0.35, p = 0.043). Additionally, in rMDD greater connectivity of the left hippocampus to the left anterior cingulate was related to higher HDRS scores (i.e., greater depression, r = 0.41, p = 0.016). The right hippocampus was more highly connected to the left middle frontal region in the rMDD group, and this relationship was not correlated with SLLT performance or HDRS scores.

Regression Analysis Using SLLT Delayed Recall Performance to Predict Hippocampal Connectivity

There were numerous significant ROIs that demonstrated a negative relationship with SLLT delayed recall performance in the HC group, covarying sex. That is, SLLT delayed recall performance was negatively associated with increasing connectivity in the right lingual gyrus and culmen of the cerebellum to the left hippocampal seed. Using the right hippocampus as the seed, a negative effect was demonstrated in multiple left medial frontal regions and in the left inferior frontal, middle and inferior temporal, and postcentral regions, as well as the right precentral and paracentral lobule, superior temporal gyrus, and uncus. Significance was also reached in bilateral putamen and the left anterior lingual gyrus of the cerebellum. Additionally, the strength of connectivity between these significant ROIs in both the HC and rMDD groups did not significantly differ in direct Fischer's t tests (see Table 5).

There were no positive relationships between SLLT delayed recall performance and HC connectivity using either the left or right hippocampal seeds. See Table 5, Figure 3.

In rMDD, sex-corrected SLLT delayed recall performance was positively associated with connectivity in the left middle temporal region when using the left hippocampal seed. Additionally, positive relationships were also demonstrated with the right hippocampal seed: the right parahippocampus/amygdala, the right claustrum, and the left putamen, as well as the right declive of the cerebellum. Similar to above, the strength of connectivity between these significant ROIs in both the HC and rMDD groups did not significantly differ in direct Fischer's t tests (see Table 5). There were no significant negative relationships in rMDD between SLLT delayed recall performance and connectivity using either the left or right hippocampal seeds. See Table 5, Figure 3.

Finally, additional regressions using the significant connectivity ROIs from Table 5 to predict SLLT delayed cued recall performance in both groups were conducted to examine the effect of scanner site. Findings reveal that site was not a significant covariate in the regression model. See Supplemental Table 1. Additionally, a principal components analysis was conducted for each group for all of the significant ROIs from Table 5, for data reduction purposes. For the HC, three factors emerged: PC1) loadings included connectivity from the right hippocampus to the left inferior and medial frontal regions, left inferior and middle temporal regions, and right putamen, PC2) loadings included connectivity from the right hippocampus to the left putamen and postcentral regions, and to the right uncus, paracentral, precentral, and superior temporal regions, and PC3) included loadings from the left hippocampal seed to the right culmen and lingual gyrus of the cerebellum and from the right hippocampal seed to the left anterior lingual gyrus of the cerebellum and the left medial frontal gyrus. For the rMDD, only one factor emerged from the PCA. These factors were then correlated with other neuropsychological measures, and results found that for HCs, PC1 negatively correlated with CVLT recognition, and Digit Symbol Coding, PC2 negatively correlated with the number of perseverative errors on the WCST, and PC3 positively correlated with Trail Making Test-Part B. In rMDD, connectivity data positively correlated with verbal fluency performance and negatively correlated with Trail Making Test-Part A. See Supplemental Table 2.

Regression Analysis Using SLLT Recognition Performance to Predict Hippocampal Connectivity

When correcting for sex, there were numerous significant ROIs that demonstrated a negative relationship with SLLT recognition performance in the HC group. That is, SLLT recognition performance was negatively associated with increasing connectivity in the right fusiform gyrus and bilateral posterior cingulate to the left hippocampal seed. Using the right hippocampus as the seed, a negative effect was demonstrated in the bilateral postcentral gyrus and putamen, as well as the right precentral, inferior frontal, superior temporal gyri, insula, precuneus. Additionally, the right hippocampal seed demonstrated a negative effect in connectivity to numerous left middle temporal regions, and to the left medial frontal and parahippocampal gyri. Of note, the strength of connectivity between the right hippocampal seed and the right inferior frontal gyrus, right insula, and left parahippocampal gyrus was

significantly different between HC and rMDD groups in direct Fischer's t tests (see Table 6). There were no positive relationships between SLLT recognition performance and HC connectivity using either the left or right hippocampal seeds. See Table 6.

In rMDD, sex-corrected SLLT recognition performance was positively associated with connectivity in bilateral fusiform gyrus when using the left hippocampal seed. Additionally, positive relationships were also demonstrated with the right hippocampal seed: the left medial frontal, fusiform, and superior temporal gyri, as well as the left amygdala and putamen, right parahippocampus and claustrum, and the right anterior culmen of the cerebellum. The strength of connectivity between these significant ROIs in both the HC and rMDD groups did not significantly differ in direct Fischer's t tests (see Table 6). There were no significant negative relationships in rMDD between SLLT recognition performance and connectivity using either the left or right hippocampal seeds. See Table 6.

Discussion

This exploratory study sought to examine the relationship between resting state functional connectivity and semantically-cued list learning performance in remitted MDD. Our results indicate that, in relation to disrupted performance on a semantically-cued episodic memory task, individuals in remission from MDD demonstrate different resting state connectivity patterns when compared to their healthy age-matched counterparts. Specifically in remitted MDD, there are hypoconnectivities between the left hippocampus and right superior frontal gyrus and between the right hippocampus and multiple fronto-temporal regions, such as the left inferior and superior frontal, left inferior temporal, and left insula, as well as the right posterior cingulate. When examining extra-network connectivity, rMDD demonstrated hyperconnectivities between the left hippocampus and multiple fronto-parietal regions and the right caudate, as well as hyperconnectivity between the right hippocampus and the left middle frontal region. By and large these decreased/increased connectivity levels in rMDD were not related to performance. Finally, regression analyses revealed that memory performance was a significant predictor of connectivity: in HCs, memory performance was a negative predictor of connectivity between the right hippocampus and multiple "in-network" fronto-temporo-parietal regions, and in rMDD memory performance positively predicted connectivity between the right hippocampus and "in-network" subcortical structures including the amygdala. So there appears to be differential connectivity patterns between in-network regions that aid performance in MDD and, surprisingly detract from performance in HC. In direct comparisons, none of these correlations for cued recall (and only two for recognition), although in opposite directions for rMDD (positive) and HC (negative) were significantly different between groups. Yet, there are also "in network" hippocampal connectivity regions that are of decreased connectivity in rMDD and "out of network" regions that are positively correlated with performance. This suggests that those rMDD who have the pattern of connectivity most similar to extra-network compensation have retained memory performance, and that lower connectivity within network is linked to poorer memory, but not in a linear fashion. These findings are consistent with previous research by Tahmasian, et al. (2013) who found reduced connectivity between the hippocampus and amygdala to the dorsomedial-prefrontal cortex and fronto-insular operculum in actively depressed individuals. In addition to these weaker connections interfering with learning and

memory, they speculated that these weaker connections may also provide a mechanism for the emergence of depressive symptoms, such as increased self-focus, that are mediated by these particular functional networks (Tahmasian, et al., 2013).

Despite experiencing minimal active depressive symptoms, those with a history of depression continue to demonstrate worse semantically-cued episodic memory than healthy controls, and show persistent disruptions of network integrity, particularly in connections to the hippocampus, after controlling for sex. Specifically, remitted MDD is associated with greater extra-network connectivities with the hippocampus when compared to controls. Interestingly, the majority of the connections that differed between groups, largely connections to frontal and cingulate regions, were not related to SLLT performance or symptom severity (Tables 3 and 4). Additionally, the in-network connections in the HC group that are negatively predictive of performance (Table 5) are not the same regions that demonstrate greater connectivity in HC relative to rMDD (Table 3), which is consistent with a stronger SLLT performance in the HC group. This would suggest a disease-specific effect on connectivity that is consistent with the literature demonstrating that depression is associated with aberrant functional connectivity in the prefrontal cortex (Sheline, et al., 2010).

Additionally, network connectivity is differentially related to memory performance in rMDD in comparison to HC. That is, resting state network connectivity in rMDD was positively predicted by episodic memory performance, though episodic memory performance was a negative predictor of network hippocampal connectivity in HCs. Given this positive relationship between network connectivity and episodic memory performance in rMDD, it is possible that this widespread pattern of hippocampal connections in rMDD may reflect compensation. In other words, those with rMDD must develop greater hippocampal connections in order to enhance their performance. Our results are consistent with previous work indicating that, in early disease course, hyperconnectivity is associated with disease resilience, or that there is a negative relationship between hippocampal connectivity and disease duration and severity (Zhang, et al., 2011). Nonetheless, individuals with rMDD, when controlled for sex, continued to perform more poorly on the task than HCs. Therefore, it remains unclear why hippocampal network integrity is differentially associated with memory performance in comparison to healthy individuals. These findings highlight how not all connectivity relationships will necessarily be additive or helpful in facilitating performance on a specific task across a backdrop of a myriad of disease and non-disease baseline functions.

In addition, sex had a small to medium effect on semantically-cued episodic memory performance. It is important that the effect of sex on verbal memory performance is not overlooked, as many previous studies have demonstrated superior verbal memory abilities in females when compared to males (e.g., Kramer et al., 2003; Lewin et al., 2001). Additionally, previous studies have also shown sex differences in semantic categorization, which our semantically-cued memory test is reliant upon (Pasterski, Zwierzynska, & Estes, 2011). Therefore, we determined that sex should be a covariate when examining behavioral performance. If males and females were combined, the increased variance would have masked important group differences. Given the exploratory nature of this study, replication

of these findings is needed, with continued scrutiny of sex differences in semantically-cued episodic memory.

One limitation of this study is that it examined resting state functional connectivity using only two seeds of interest, the left and right hippocampus; however, it is clear that memory performance, especially in MDD, is mediated by multiple other brain regions in the Papez circuit (Papez, 1937). Additionally, given the cross-sectional nature of this study, we are unable to make specific predictions about whether resting state connectivity patterns during remission are associated with future depressive episodes or memory impairment. Therefore, following these at-risk individuals over time will likely provide greater insight into protective versus risk factors. Finally, it is worth noting that although our remitted MDD participants were not actively depressed according to out diagnostic interview, their scores on the self-administered HDRS did reveal significantly higher scores than the healthy control group. Although this two-point elevation is not clinically significant, it is possible that these remitted MDD individuals may have demonstrated different connectivity to performance relationships while actively depressed, and may still exhibit residual differences in these relationships at the time of this evaluation. Further analyses with a larger sample may help to reduce the discrepancy in symptom severity.

Of note, the memory test utilized for this study, the SLLT, was selected for its potential clinical application, seeing as how the one-trial learning is a format that more closely follows that observed in real life (i.e., single verbal instruction for a list of items to purchase at the grocery story). It is atypical to more traditional memory probes of repeated list learning, tests designed to test for impaired consolidation and rapid forgetting in the context of dementia (Delis, et al., 2000, Schmidt, 1996).

Overall, this exploratory study suggests that even when no overt depressive symptoms are present, and when controlling for sex, individuals with a history of depression demonstrate disruptions in their semantically-cued episodic memory, as well as disruptions in hippocampal connectivity. Additionally, there is a differential relationship between hippocampal network integrity and semantically-cued episodic memory performance in those with rMDD when compared to healthy individuals, which is intriguing and requires replication and further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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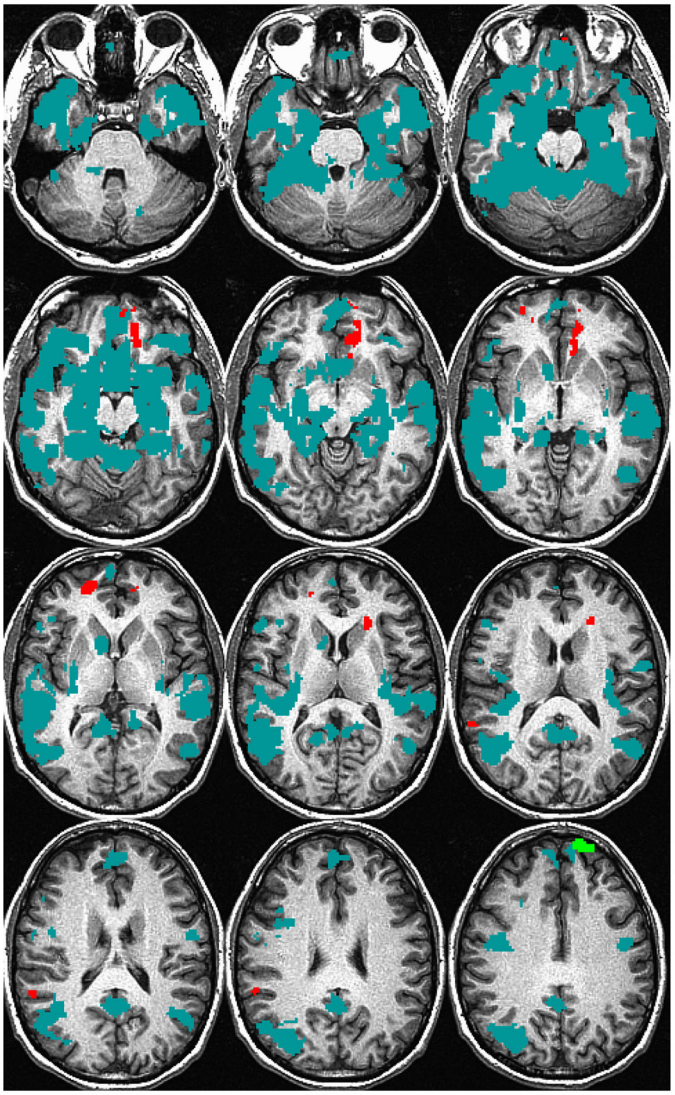

Figure 1.
Whole Group Baseline Connectivity Covaried by Sex, Left Hippocampal Seed. Combined HC and rMDD connectivity (aqua); HCs demonstrating greater connectivity than rMDD within network (lime green); rMDD demonstrating greater connectivity than HCs extra-network (red).

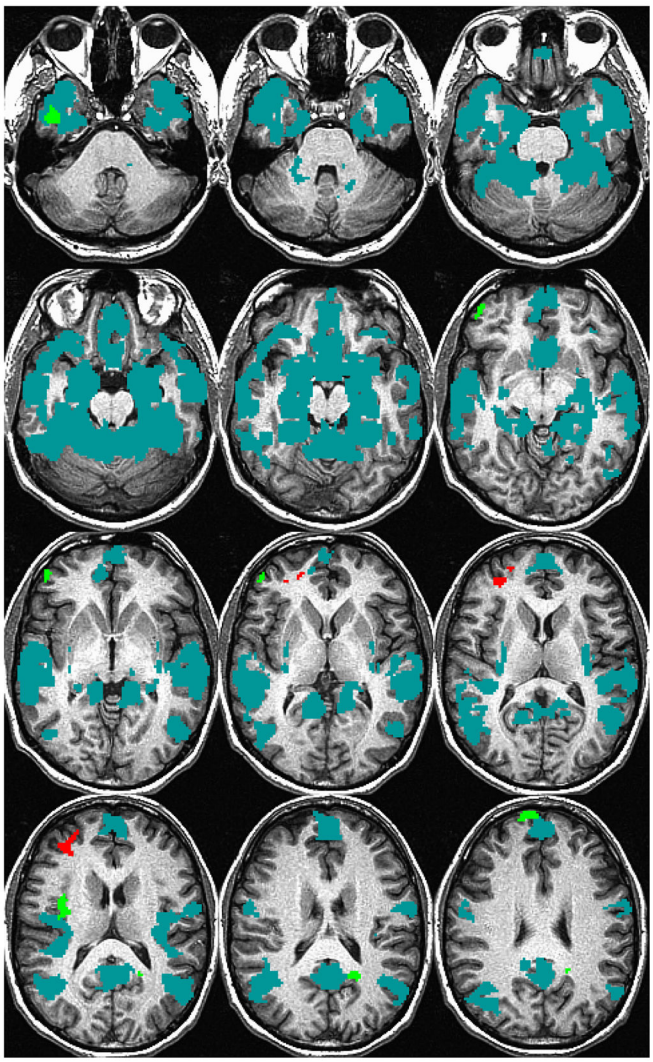

Figure 2.

Whole Group Baseline Connectivity Covaried by Sex, Right Hippocampal Seed. Combined HC and rMDD connectivity (aqua); HCs demonstrating greater connectivity than rMDD within network (lime green); rMDD demonstrating greater connectivity than HCs extra-network (red).

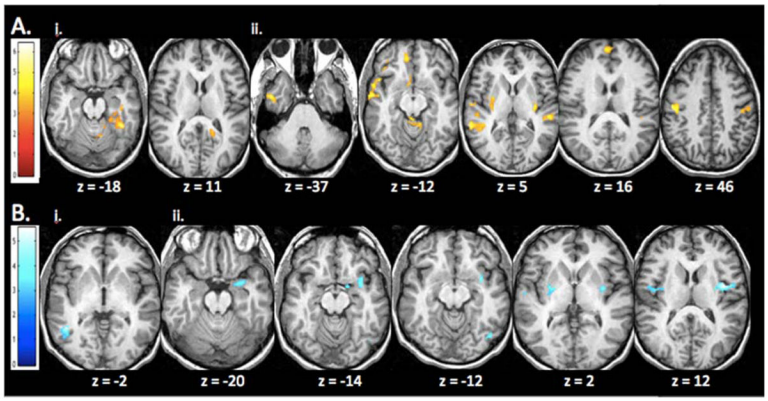

Figure 3.

Predicting Connectivity from SLLT Performance by Group using Sex corrected Cued Recall-False Positive scores. Panel A represents HC resting state connectivity pattern for negative cued recall for the i) left hippocampal seed and ii) the right hippocampal seed. Panel B represents resting state connectivity pattern in rMDD for positive cued recall for the i) left hippocampal seed and ii) the right hippocampal seed.

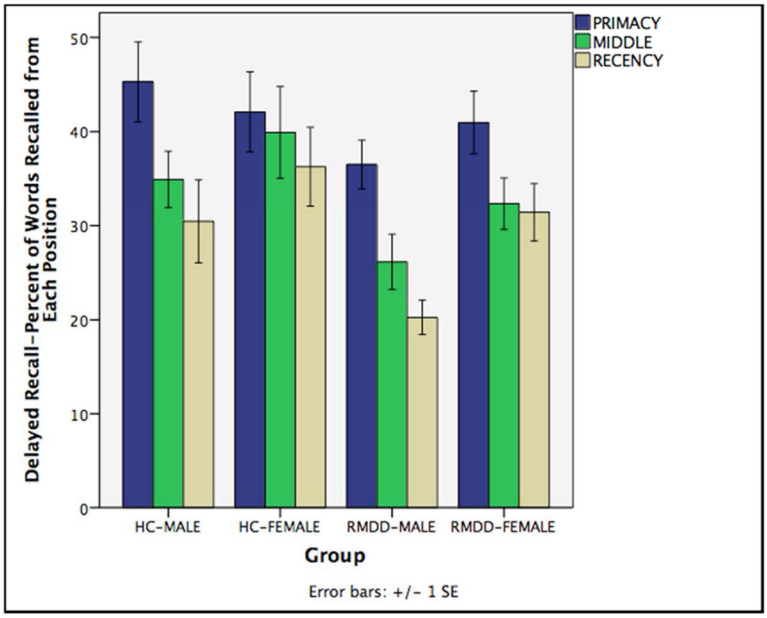

Figure 4.
Recall Serial Position Curve of the SLLT by Group and Gender.

Table 1

Demographic and Clinical Information by Group.

	rMDD (n = 34) ***M (SD)***	**HCs (n = 23)** ***M (SD)***	***p*** ***(r^2)***
Age	21.1 (1.5)	21.1 (1.5)	0.863
Sex (M/F)	9/25	11/12	0.097
Education	14.4 (1.4)	14.9 (1.1)	0.197
Estimated Verbal IQ[1]	104.1 (8.8)	102.4 (10.1)	0.662
HDRS	2.4 (2.8)	0.4 (1.0)	0.002* (0.16)
Number of Depressive Episodes	1.9 (1.2)	--	--
Mean Age of Onset	15.8 (3.1)	--	--
Participants with a History of Psychiatric Hospitalization	3	--	--

Note.

*This mean difference was statistically significant, although clinically these are very low symptom levels (below 7 is consider full remission).

[1]Estimated from the Shipley-2 Verbal subtest administered in Superlab.

Table 2

SLLT and Neuropsychological Test Performance Raw Data by Group, means and standard deviations.

	rMDD			HC			rMDD v. HC	
Memory	***Male***	***Female***	***Total***	***Male***	***Female***	***Total***	***p***	**Cohen's *d***
SLLT								
Delayed Cued Recall (Hits-False Positives)	39.8 (17.1)	49.0 (25.5)	46.6 (23.7)	57.1 (20.8)	64.8 (21.8)	61.1 (21.2)	**0.02**	0.65
Recognition (Hits-False Positives)	34.8 (16.2)	41.5 (29.1)	39.7 (26.2)	52.7 (23.9)	59.5 (23.2)	56.3 (23.3)	**0.02**	0.67
Delayed Cued Recall d′	1.6 (0.7)	1.5 (0.6)	1.5 (0.6)	1.9 (0.8)	1.8 (0.5)	1.8 (0.6)	0.08	
Delayed Recognition, d′	1.5 (0.4)	1.6 (0.6)	1.6 (0.6)	1.7 (0.5)	1.8(0.6)	1.8 (0.5)	0.11	
CVLT-II								
Long Delay Free Recall	13.4 (2.2)	13.9 (2.4)	13.8 (2.3)	13.8 (1.5)	13.8 (1.9)	13.8 (1.7)	0.94	
Recognition	15.2 (1.2)	15.6 (0.8)	15.5 (1.0)	15.1 (1.4)	15.6 (0.5)	15.4 (1.0)	0.74	
Language								
Verbal Fluency								
Letter	42.0 (6.1)	46.1 (13.1)	45.0 (11.5)	39.6 (7.3)	43.4 (9.4)	41.6 (8.5)	0.26	
Animals	22.0 (5.1)	23.0 (3.8)	22.7 (4.2)	20.6 (2.7)	21.8 (5.4)	21.2 (4.3)	0.21	
Visuospatial								
Benton Visual Form Discrimation	30.0 (2.4)	30.5 (1.6)	30.3 (1.8)	30.0 (2.2)	30.0 (3.5)	30.0 (2.4)	0.68	
Motor								
Purdue Pegboard								
Bilateral Average	10.3 (2.4)	10.5 (1.7)	10.4 (1.9)	9.9 (2.5)	10.8 (1.5)	10.3 (2.1)	0.82	
Digit Symbol Coding	78.7 (17.7)	83.6 (7.1)	82.2 (11.2)	82.4 (13.8)	88.2 (14.0)	85.4 (13.9)	0.34	
Trail Making Test- A	21.2 (6.8)	22.0 (7.0)	21.7 (6.8)	23.4 (9.1)	20.9 (5.1)	22.1 (7.2)	0.85	
Executive Functioning								
Trail Making Test- B	44.0 (14.1)	50.3 (16.4)	48.4 (15.8)	55.6 (9.5)	50.2 (7.4)	52.8 (15.9)	0.33	
Stroop								
Interference (*T*)	59.0 (7.4)	55.4 (6.7)	56.5 (7.0)	56.2 (9.5)	58.7 (5.0)	57.5 (7.4)	0.60	
Wisconsin Card Sorting Test								
Total Correct	75.4 (13.0)	71.7 (8.1)	72.8 (9.8)	72.9 (9.9)	76.0 (9.6)	74.5 (9.7)	0.52	

Memory	rMDD			HC			rMDD v. HC	
	Male	*Female*	*Total*	*Male*	*Female*	*Total*	*p*	Cohen's *d*
Perseverative Errors	8.3 (3.2)	9.8 (5.5)	9.3 (4.9)	9.0 (5.8)	10.5 (9.1)	9.8 (7.6)	0.81	

Table 3

Within Network Differences in Sex-Corrected Resting State Connectivity between Remitted MDD and Healthy Control and Relationship to Sex-Corrected SLLT Delayed Cued Recall (DCR) and Recognition (Recog) Performance.

			MNI Coordinates					Correlations (r)		
Lobe	**Region**	**BA**	**x**	**y**	**z**	**Z**	**mm^3**	**SLLT DC Recall**	**SLLT DC Recog**	**HDRS**
Decreased in rMDD								rMDD (HC)	rMDD (HC)	rMDD
Left Hippocampus										
Frontal	Superior Frontal	9	12	62	36	3.8	608	−.04(.12)	−.05(.12)	−.30
Right Hippocampus										
Frontal	Middle Frontal	10	−46	52	−6	3.5	584	−.01(.07)	.05(.11)	.18
	Superior Frontal	9	−12	66	28	4.1	576	.03(.46*)	.02(.48*)	.28
Temporal	Inferior Temporal	20	−42	−6	−36	3.4	608	.03(−.21)	−.01(−.16)	−.11
Parietal	Posterior Cingulate	30	22	−54	22	3.6	480	−.15(−.39)	−.18(−.41)	.12
		31	14	−38	30	3.7	472	.01(−.38)	−.04(−.38)	−.11
Subcortical	Claustrum	--	−34	−8	18	3.7	536	.19(−.27)	.16(−.25)	−.09
Increased in rMDD										
Left Hippocampus										
None										
Right Hippocampus										
None										

*Denotes $p < .05$

Table 4

Extra-Network Differences in Sex-Corrected Resting State Connectivity between Remitted MDD and Healthy Control and Relationship to Sex-Corrected SLLT Delayed Cued Recall (DCR) and Recognition (Recog) Performance.

			MNI Coordinates					Correlations (r)		
Lobe	**Region**	**BA**	**x**	**y**	**z**	**Z**	**mm^3**	**SLLT DC Recall**	**SLLT DC Recog**	**HDRS**
Decreased in rMDD								rMDD (HC)	rMDD (HC)	rMDD
Left Hippocampus										
None										
Right Hippocampus										
None										
Increased in rMDD										
Left Hippocampus										
Frontal	Anterior Cingulate	32	14	34	−12	3.5	2208	.35*(−.23)	.36*(−.21)	.27
		32	−20	50	4	3.7	1448	.07(−.25)	.15(−.25)	.41*
	Paracentral Lobule	5	−20	−34	58	3.5	1168	.03(−.18)	.14(−.19)	.32
	Medial Frontal	9	10	54	22	3.4	488	.04(−.20)	.02(−.19)	.06
	Middle Frontal	9	−38	24	24	3.1	464	.17(.22)	.11(.23)	−.01
Temporal	Superior Temporal	22	−60	−46	20	3.9	1160	.13(−.05)	.17(−.02)	.23
Parietal	Posterior Cingulate	31	28	−22	48	3.7	1000	.15(.04)	.19(.02)	.29
	Supramarginal	40	28	−38	58	3.1	728	.23(−.16)	.35*(−.15)	.20
Right Hippocampus										
Frontal	Middle Frontal	10	−36	42	14	4.2	2800	.14(.04)	.22(.06)	.16

*Denotes $p < .05$.

Table 5

Regression analysis predicting Connectivity from SLLT delayed cued recall scores (sex-corrected), using an in-network (HC) mask.

				MNI Coordinates					
ROI #	**Lobe**	**Region**	**BA**	**x**	**y**	**z**	**Z**	**mm^3**	**Fischer's Z- test *p* (HC vs rMDD)**
HC									
Positive Recall									
Left Hippocampus									
	None								
Right Hippocampus									
	None								
Negative Recall									
Left Hippocampus									
1.	Occipital	Lingual/Postcentral	19/30	16	−48	6	3.69	848	0.47
2.	Cerebellum	Culmen	--	42	−46	−20	4.36	3096	0.48
3.			--	12	−50	−14	4.66	752	0.49
Right Hippocampus									
4.	Frontal	Medial Frontal	10	−8	42	−16	3.77	1008	0.46
5.			25	−6	12	−16	4.13	848	0.46
6.			9	−4	56	16	3.37	528	0.49
7.		Precentral	4	50	−12	60	3.6	944	0.46
8.		Paracentral Lobule	6	2	−26	68	2.97	736	0.45
9.		Inferior Frontal	47	−42	24	−22	3.59	704	0.49
10.	Temporal	Middle Temporal	21	−60	8	−14	4.37	4328	0.50
11.			22	−66	−42	8	4.31	2752	0.48
12.		Superior Temporal	41	44	−38	12	4.04	2040	0.45
13.		Inferior Temporal	20	−50	−2	−38	3.88	1096	0.40
14.		Uncus	34	14	2	−24	3.48	448	0.44
15.	Parietal	Postcentral	2	−48	−20	40	3.94	1504	0.44
16.	Subcortical	Putamen	--	−30	−2	6	3.18	544	0.46
17.			--	32	−18	4	3.95	528	0.46
18.	Cerebellum	Anterior Lingual	--	−2	−38	−12	3.32	512	0.46

				MNI Coordinates					
ROI #	**Lobe**	**Region**	**BA**	**x**	**y**	**z**	**Z**	**mm^3**	**Fischer's Z- test *p* (HC vs rMDD)**
rMDD									
Positive Recall									
Left Hippocampus									
19.	Temporal	Middle Temporal	37	−48	−54	−2	4.57	880	0.46
Right Hippocampus									
20.	Temporal	Parahippocampal	34	34	4	−14	3.64	1000	0.46
21.	Subcortical	Claustrum	--	42	−2	12	4.4	1696	0.43
22.		Putamen	--	−34	−20	6	3.84	1336	0.45
23.	Cerebellum	Declive	--	48	−72	12	3.24	480	0.44
Negative Recall									
Left Hippocampus									
	None								
Right Hippocampus									
	None								

Table 6

Regression analysis predicting Connectivity from SLLT recognition scores (sex-corrected), using an in-network (HC) mask.

				MNI Coordinates					
ROI #	**Lobe**	**Region**	**BA**	**x**	**y**	**z**	**Z**	**mm^3**	**Fischer's Z- test *p* (HC vs rMDD)**
HC									
Positive Recognition									
Left Hippocampus									
	None								
Right Hippocampus									
	None								
Negative Recognition									
Left Hippocampus									
1.	Temporal	Superior Temporal	22	56	−32	10	4.26	616	0.94
2.	Parietal	Posterior Cingulate^	30	−14	−58	18	3.51	952	0.31
3.			30	20	−50	14	3.85	896	0.54
Right Hippocampus									
4.	Frontal	Precentral Gyrus^	6	32	−12	60	3.79	608	0.28
5.		Medial Frontal^	9	−4	56	14	3.3	536	0.80
6.		Inferior Frontal	44	62	4	22	3.78	488	0.02*
7.	Temporal	Middle Temporal	39	−58	−62	16	3.94	3176	0.28
8.		^	21	−62	−4	−10	4.05	1384	0.39
9.		^	22	−64	−44	8	3.73	632	0.99
10.		Superior Temporal^	41	50	−36	12	4.47	1936	0.33
11.		Insula	13	48	−16	22	3.99	584	0.02*
12.	Temporal	Parahippocampal	28	−22	−14	−20	3.68	568	0.37
13.			19	−18	−48	−2	3.62	552	0.04*
14.	Parietal	Precuneus^	7	14	−38	60	3.82	2704	0.44
15.		Postcentral	2	44	−22	38	3.64	2096	0.69
16.		^	2	−48	−22	40	4.15	1872	0.24
17.	Subcortical	Putamen^	--	−32	−16	8	3.24	456	0.22

				MNI Coordinates					
ROI #	**Lobe**	**Region**	**BA**	**x**	**y**	**z**	**Z**	**mm^3**	**Fischer's Z- test *p* (HC vs rMDD)**
18.		^	--	36	−16	2	3.49	448	0.33
rMDD									
Positive Recognition									
Left Hippocampus									
19.	Occipital	Fusiform ^	19	−48	−68	−8	3.55	2848	0.60
20.			19	44	−70	−8	3.56	1488	0.63
Right Hippocampus									
21.	Frontal	Medial Frontal	10	−8	58	0	3.45	840	0.74
22.	Temporal	Fusiform	20	−44	−36	−14	4.09	3312	0.84
23.		Parahippocampal ^	34	34	4	−14	4.68	2544	0.43
24.		Superior Temporal	22	−56	−6	6	3.64	1528	0.88
25.	Subcortical	Claustrum ^	--	42	−4	12	4.68	3024	0.17
26.		Amygdala	--	−30	2	−18	3.69	1296	0.33
27.		Putamen ^	--	−16	22	−8	4.1	504	0.71
28.	Cerebellum	Anterior Culmen	--	38	−52	−22	3.86	3512	0.32
Negative Recognition									
Left Hippocampus									
	None								
Right Hippocampus									
	None								

^ Regions of significant overlap with the regions reported in Table 5 (recall).

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