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Altered brain function underlying verbal memory encoding and retrieval in psychotic major depression

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Abstract

Psychotic major depression (PMD) is associated with deficits in verbal memory as well as other cognitive impairments. This study investigated brain function in individuals with PMD during a verbal declarative memory task. Participants included 16 subjects with PMD, 15 subjects with non-psychotic major depression (NPMD) and 16 healthy controls (HC). Functional magnetic resonance imaging (fMRI) data were acquired while subjects performed verbal memory encoding and retrieval tasks. During the explicit encoding task, subjects semantically categorized words as either “man-made” or “not manmade.” For the retrieval task, subjects identified whether words had been presented during the encoding task. Functional MRI data were processed using *SPM5* and a group by condition ANOVA. Clusters of activation showing either a significant main effect of group or an interaction of group by condition were further examined using *t*-tests to identify group differences. During the encoding task, the PMD group showed lower hippocampus, insula, and prefrontal activation compared to HC. During the retrieval task, the PMD group showed lower recognition accuracy and higher prefrontal and parietal cortex activation compared to both HC and NPMD groups. Verbal retrieval deficits in PMD may be associated with deficient hippocampus function during encoding. Increased brain activation during retrieval may reflect an attempt to compensate for encoding deficits.

Keywords

Depression; Psychosis; Functional imaging; Verbal declarative memory; Hippocampus; Encoding deficits

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Appendix A. Supporting information Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.psychresns.2012.06.008>.

1. Introduction

Depression can be regarded as a heterogeneous condition, likely consisting of various subtypes associated with family psychiatric history, cognitive profiles and clinical features (Keller et al., 2007; Carragher et al., 2009). It has been estimated that 1 in 6 individuals with major depression also demonstrate psychotic features (psychotic major depression; PMD) (Johnson et al., 1991; Parker et al., 1992; Ohayon and Schatzberg, 2002). Nosological data have emerged since the early 1980s suggesting PMD and non-psychotic major depression (NPMD) are, indeed, separate subtypes of depression (Keller et al., 2007). PMD is associated with greater duration and severity of symptoms compared to NPMD (Nelson and Charney, 1981; Rothschild et al., 1989; Fleming et al., 2004; Keller et al., 2006; Maj et al., 2007). Additionally, individuals with PMD show greater cognitive deficits in verbal memory, attention and executive functioning compared to NPMD (Basso and Bornstein, 1999; Schatzberg et al., 2000; Fleming et al., 2004; Gomez et al., 2006). A recent functional brain imaging study (Garrett et al., 2011) identified aberrant working memory networks in PMD compared to NPMD and HC groups.

Several studies have identified verbal memory deficits in PMD (Schatzberg et al., 2000; Fleming et al., 2004; Hill et al., 2004; Gomez et al., 2006; Zanelli et al., 2010). Two recent studies suggest that impaired encoding of verbal memory may be responsible for recognition memory deficits in PMD (Gomez et al., 2006; Zanelli et al., 2010). Similarly, a review of verbal declarative memory studies in schizophrenia concluded that deficits occur primarily during encoding, and are likely to involve prefrontal-hippocampal circuits (Cirillo and Seidman, 2003). It is possible that deficits in similar brain circuits during encoding underlie verbal memory deficits in PMD as well.

The hippocampus is heavily resourced during verbal declarative memory encoding (Schacter and Wagner, 1999; Menon et al., 2002; Greicius et al., 2003; Parsons et al., 2006; Spaniol et al., 2009) and, to a lesser extent, during verbal declarative memory retrieval (Spaniol et al., 2009). Across the literature on hippocampus function during memory tasks in subjects with depression, activation deficits have been observed during encoding (Bremner et al., 2004; Fairhall et al., 2010; Milne et al., 2011), except for an associative learning paradigm that instead found increased parahippocampal activation (Werner et al., 2009). While less common, memory retrieval in depression has also been associated with lower hippocampus activation (Werner et al., 2009; Fairhall et al., 2010; Milne et al., 2011). Hippocampal dysfunction could also play a role in verbal memory deficits in PMD (Gomez et al., 2006). Although, gross hippocampal volume reductions have not been observed in PMD (Keller et al., 2008) hippocampal dysfunction could still exist (Czeh and Lucassen, 2007). Alternately, other components of the verbal memory encoding network may be responsible for deficits in recognition, such as the prefrontal cortex. Reviews of the memory encoding literature conclude that activation of the ventrolateral prefrontal cortex is associated with selecting and maintaining incoming information while activation of the dorsolateral prefrontal cortex is associated with organizing and forming associations between items during encoding (Blumenfeld and Ranganath, 2007; Binder et al., 2009; Spaniol et al., 2009).

Using functional magnetic resonance imaging (fMRI), we hypothesized that individuals with PMD would demonstrate altered profiles of activation during encoding (but not retrieval) of verbal information, particularly within the hippocampus and prefrontal cortex. Such findings would suggest that verbal memory retrieval deficits in PMD are primarily associated with encoding deficits.

2. Methods

2.1. Subjects

Twenty-four subjects with PMD, nineteen subjects with NPMD and twenty-one HC subjects were initially included in this analysis. After screening for exclusionary criteria (see below), sixteen subjects with PMD, fifteen subjects with NPMD and sixteen HC subjects were included in the final fMRI analysis. The Stanford University Institutional Review Board approved the study and all subjects gave written consent before participation. Subjects with PMD and NPMD were recruited through inpatient and outpatient facilities at Stanford University Medical Center or self-referred from advertisements. Healthy controls were recruited from the community through advertisements.

Subjects with PMD and NPMD met the following inclusion criteria: (1) a minimum score of 21 on the 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), (2) a score of 7 or higher on 7 items of the core endogenomorphic scale (Thase et al., 1983), and (3) current unipolar major depressive episode, with or without psychotic features, based on the DSM-IV criteria. Moreover, PMD was differentiated from NPMD by a minimum score of 5 on the positive symptoms subscale of the Brief Psychotic Rating Scale (BPRS) (Gorham and Overall, 1961). When relevant, subjects were permitted to continue medications for ethical and safety reasons; all medications were required to be stable for one-week prior to study entry (Table 1). Healthy controls met the following inclusion criteria: (1) score of less than 6 on the HDRS, (2) no psychotic symptoms as measured by the BPRS, and (3) no past or present psychiatric disorders as determined by the Structural Clinical Interview for DSM-IV-TR Axis I Disorders (First MB et al., 1997).

Subjects were excluded from the study if they had a major medical illness, a history of seizures, previous head trauma, unstable or untreated hypertension, a history of substance abuse, were actively suicidal, met criteria for obsessive compulsive disorder or bipolar I or II disorder, were pregnant or lactating, were less than 18 years of age, or had electroconvulsive therapy within the last 6 months. Subjects taking estrogen supplements or hormonal contraceptives were excluded because of known interactions between cortisol and estrogen and potential confounding effects on brain function during semantic retrieval (Kuhlmann and Wolf, 2005; Konrad et al., 2008).

Subjects who were recruited into the study, were later excluded from the fMRI analysis if performance was below chance (50% accuracy) on the recognition of encoded words during the retrieval task. A subject's functional MRI data were excluded if more than 25% of the time points exceeded a 0.5 mm/TR motion threshold or had global signal greater than 3% from the mean global signal of all images as determined by *ArtRepair* (<http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm>).

2.2. Verbal declarative memory tasks

The encoding task presented alternating blocks of encoding and control epochs and had a duration of 5'56". The five encoding epochs each presented eight nouns for 2.5 s with a 0.5 s interstimulus interval. To enhance encoding (Craik et al., 1994), subjects were instructed to classify each noun into one of two semantic categories, "man-made" or "not man-made". Subjects indicated their response by pressing one of two buttons. The two semantic categories were represented equally across each encoding epoch. Subjects were aware that there would be a subsequent retrieval task. The five control epochs alternated the presentation of the same two words 8 times subjects were instructed to alternate pressing one of two buttons for each word presented without making a semantic discrimination. Each epoch was preceded by a 4 s written instruction. A 24-s rest epoch with fixation occurred at

the beginning, end, and mid-point of the task. This task has been described in previous studies from our group (Greicius et al., 2003; Carrion et al., 2009).

The retrieval task presented alternating blocks of retrieval and control epochs and had a duration of 6'52". In total, 32 previously-encoded words and 16 novel words were shown across 6 retrieval epochs. During each retrieval epoch nouns were presented for 2.5 s with a 0.5 s interstimulus interval. Subjects were instructed to press one of two buttons to identify whether the word had or had not been presented during the encoding task. Each retrieval epoch was followed by a control epoch presenting the same two alternating words from the encoding task. Subjects were instructed to alternate between the two buttons for each word presented regardless of recognition judgment. A 24 s rest epoch with fixation was presented at the beginning, end, and mid-point of the task. Subjects completed a 5-min scan (with gonogo task) between the encoding and retrieval tasks in order to reduce the likelihood of rehearsal. The tasks were presented using Psyscope software (<http://psy.ck.sissa.it>).

2.3. Behavioral data analysis

Measures of task performance collected during scanning included response accuracy and response time for each stimulus (Table 2). For the encoding task, accuracy was the percentage of correct semantic categorizations; corrected accuracy for the retrieval task was calculated by hit rate minus false alarm rate, where hit rate=number correctly recognized words/ total number encoding words and false alarm rate=number of novel words incorrectly recognized/ total number of encoding words. A signal detection applet (http://wise.cgu.edu/sdtmod/signal_applet.asp) was used to calculate recognition discriminability (d'). Behavioral data were analyzed using *SPSS* 17 (<http://www.spss.com/software/statistics>). A 3-group ANOVA was used to test for group differences in accuracy and response time. Significant ANOVAs ($p < 0.05$) were followed by 2-group post hoc analyses.

2.4. fMRI data acquisition

Functional data were collected on a 3T GE Signa scanner using a GE whole head coil (L_x platform, gradients 40 mT/m, 150 T/m/s; GE Medical Systems, Milwaukee, Wisconsin). Twenty-eight axial slices (4 mm thick, 0.05 mm skip), parallel to the axis of anterior and posterior commissures and covering the entire brain ($FOV = 200 \text{ mm}^2$, 64×64 matrix with an inplane spatial resolution $= 3.125 \text{ mm}^2$) were acquired using a T2 weighted gradient echo spiral pulse sequence with the following parameters: $TR = 2000 \text{ ms}$, $TE = 30 \text{ ms}$, flip angle $= 89$ degrees and one interleave (Glover and Lai, 1998). Magnetic field inhomogeneities were reduced by a shimming protocol used before acquiring fMRI scans (Spielman et al., 1998).

2.5. fMRI data analysis

Functional data were preprocessed and statistically analyzed using *SPM5* (<http://www.fil.ion.ucl.ac.uk/spm>). After scanning, images were reconstructed, resampled to 2 mm isotropic voxels and spatially realigned to the third volume, which was chosen to avoid magnetic susceptibility artifacts. Interpolation errors caused during image realignment were corrected using voxel-wise amplitudemotion correlations (Grooten et al., 2000). The image distortion and spin history errors caused by abrupt motions were repaired by interpolation from the nearest unaffected volumes. These methods were implemented in the *ArtRepair* software toolbox for SPM (<http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm>). Data were spatially normalized into standard stereotactic space using the MNI (Montreal Neurological Institute) echo-planar image template provided by *SPM5*. Normalized images were then smoothed with a 7 mm FWHM Gaussian filter.

Statistics at the individual level used a fixed effects block design model to define experimental (encoding and retrieval) and control conditions. A high-pass filter of 120 s was

applied to the data. Contrasts included encoding minus control and retrieval minus control for the encoding and retrieval tasks, respectively. Functional region of interest (ROI) clusters were initially defined using a random effects model and a multivariate ANOVA analysis as implemented in SPM5. A 2-way ANOVA with factors group (PMD, NPMD, and HC) and task (encoding minus control and retrieval minus control) was used to identify activation differences among the three groups (main effect of group) and regions that showed different task effects per group (interaction between group and task). For this initial step, we applied an exploratory threshold (height $p < 0.001$ and extent of 10 voxels), intended to identify activation differences among the 3 groups. We expect the PMD and NPMD groups to share some abnormalities compared to the healthy control group, and a more stringent cluster corrected threshold would be likely to eliminate these common abnormalities. In the second step, we conducted follow-up t -tests of clusters identified in the first step. Clusters were required to reach significance criteria and also to be relevant to previous neuroimaging studies of patients with PMD or NPMD. Activation (mean T-score) was extracted using the *MarsBar* toolbox (<http://marsbar.sourceforge.net/>) and exported to *SPSS* software, where independent group t -tests, covaried for task accuracy, were used to identify group differences, with Bonferroni correction for multiple comparisons.

To identify neuroanatomical locations, activation clusters were superimposed on a single-subject high-resolution T1-weighted image. Additionally, activation cluster coordinates were converted from MNI space into Talairach space (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach/>) and input into a Talairach daemon (<http://www.nitrc.org/projects/tal-daemon/>) to help identify neuroanatomical locations.

3. Results

3.1. Subjects

Five subjects with PMD, two with NPMD and two HC were excluded from the analysis due to retrieval task accuracy below 50%. Three subjects with PMD, two with NPMD and three HC were excluded due to excessive motion during one of the functional imaging verbal memory tasks. Included in the final analysis are 16 PMD (8 females), 15 NPMD (8 females), and 16 HC (7 females) subjects. The groups were not significantly different in age, gender, handedness, or years of education. Additionally, the groups had similar IQ ($p = 0.60$), as measured by the Wechsler Test of Adult Reading (WTAR) (2001) full scale estimate of premorbid intellectual function.

3.2. Verbal declarative memory performance

Significant group differences were observed for corrected accuracy of recognized words ($F(1,47) = 4.80$, $p = 0.013$). Two-group post hoc analyses indicated significantly lower corrected accuracy for recognized words in the PMD group compared to the HC group ($t(30) = -2.91$, $p = 0.007$) and the NPMD group ($t(29) = -2.15$, $p = 0.04$) (Table 2). Therefore, fMRI analyses of verbal encoding and retrieval were covaried for recognition accuracy. No other measures of task performance were significantly different between groups including false alarm rate and d' .

3.3. fMRI—main effect of group

The main effect of group across retrieval and encoding contrasts identified 2 clusters of activation: right anterior cingulate and left parietal (Table 3, Fig. 1). Post-hoc t -tests found that sub-gyral right anterior cingulate differences was attributed to higher activation in the HC group compared to both PMD ($p = 0.001$ and $p = 0.009$) and NPMD ($p = 0.010$ and $p = 0.003$) groups in both encoding and retrieval tasks, respectively. No significant right anterior cingulate activation differences were observed between PMD and NPMD groups.

Group comparisons of left parietal lobule activation found the PMD group to have significantly higher activation compared to both HC ($p<0.001$) and NPMD ($p=0.013$) groups exclusively in the retrieval task. No significant left parietal lobule activation differences were observed between HC and NPMD groups in either encoding or retrieval tasks.

3.4. fMRI—interaction of group by task

The interaction of group by task identified by the ANOVA resulted in 10 significant clusters of activation (Table 3, Fig. 2). Post-hoc t -tests were conducted on 6 clusters that were selected based on previous literature implicating aberrant hippocampus, prefrontal cortex and insular function in depression (Liotti et al., 2002; Werner et al., 2009; Fairhall et al., 2010; Sprengelmeyer et al., 2011; Garrett et al., 2011; Milne et al., 2011; Hamilton et al., 2012). During the encoding task the PMD group had significantly lower activation compared to HC in the right hippocampus ($t=3.15$, $p=0.007$), and left middle frontal gyrus ($t=3.80$, $p=0.001$), while activation differences from left insula ($p=0.018$), right insula ($p=0.016$), left hippocampus ($t=2.18$, $p=0.027$) approached significance. Additionally, the PMD group had significantly lower activation in the right insula ($t=3.00$, $p=0.003$) compared to the NPMD group during encoding. Higher activation in HC group compared to NPMD group approached significance in the left hippocampus, ($t=2.57$, $p=0.009$), left insula ($p=0.044$), and left superior dorsolateral frontal gyrus ($p=0.038$) during encoding. The PMD group exhibited higher activation approaching significance during the retrieval task in the right dorsolateral prefrontal cortex compared to HC ($p=0.031$) and in the left middle frontal gyrus compared to NPMD ($p=0.032$).

4. Discussion

In this study we investigated brain function related to encoding and retrieval of verbal information in carefully characterized groups of individuals with PMD compared to those with NPMD and HC. As expected, the PMD group had impaired memory retrieval compared to the HC and NPMD groups. After adjusting for recognition accuracy, fMRI results indicated hippocampus, insula and prefrontal cortical deficits in the PMD group during encoding, possibly associated with inefficient organization and association of incoming information. The PMD group also showed relatively greater prefrontal and parietal cortex activation during retrieval, possibly reflecting a compensatory response in the face of encoding deficits. These findings support the hypothesis that verbal memory retrieval deficits in PMD stem from aberrant brain function during encoding.

The profile of activation within the HC group during the encoding task is largely compatible with previously described models of verbal and semantic memory, including left hemisphere activation in the inferior frontal cortex, hippocampus, fusiform gyrus, and middle occipital gyrus (Wagner et al., 1998; Casasanto et al., 2002; Kraut et al., 2004; Davachi and Dobbins, 2008; Spaniol et al., 2009) (Table S2, online supplemental material). Thus, we are confident that the task was valid for testing our primary hypothesis. The PMD and NPMD groups also showed activation in these networks, including the left prefrontal cortex and visual areas. For the retrieval task, all three groups activated the bilateral inferior frontal gyri and the visual cortex, consistent with previous literature on verbal memory retrieval (Ragland et al., 2000; Habib et al., 2003; Spaniol et al., 2009) (Table S3, online supplemental material). Several brain regions, including the left inferior frontal gyrus, are activated during both encoding and retrieval and may represent an overarching semantic memory network (Nyberg et al., 2003; Binder et al., 2009).

Hippocampal activation during encoding was observed within the HC group, consistent with previous studies from our lab using the same task (Menon et al., 2002; Greicius et al., 2003). Our results of hippocampus dysfunction during memory encoding in PMD and NPMD

support previous findings (Bremner et al., 2004; Fairhall et al., 2010). These activation deficits are located in the anterior hippocampal head, which has been shown to be associated with successful memory encoding in subjects with depression (Fairhall et al., 2010). Hippocampus activation deficits in depression have also been observed during memory retrieval (Milne et al., 2011); however, our results support deficits only during encoding. Hypercortisolemia connected to PMD (Schatzberg et al., 1983; Rothschild et al., 1987; Nelson and Davis, 1997; Belanoff et al., 2001; Gomez et al., 2009) and NPMD (Lok et al., 2011) might have detrimental effects on hippocampus function (Sapolsky, 2000).

Group differences in activation suggest neural deficits in the prefrontal cortex in the PMD group during encoding, including portions of the left prefrontal cortex. Previous studies of verbal memory encoding in individuals with schizophrenia (Ragland et al., 2004) and those at risk for psychosis (Allen et al., 2009) have suggested that weak prefrontal cortex activations are attributable to inefficient organizational encoding strategies. This interpretation is consistent with the idea that the prefrontal cortex is responsible for organizing and forming associations between items during encoding (Blumenfeld and Ranganath, 2007; Binder et al., 2009; Spaniol et al., 2009). Thus, verbal retrieval deficiencies in the PMD group may be related to inefficient organization of information during encoding.

Activation deficits near the anterior cingulate cortex during memory encoding and retrieval in the PMD and NPMD groups might represent shared pathophysiology. Our results also corroborate previously reported anterior cingulate cortex activation deficits in NPMD during encoding (Bremner et al., 2004).

Insular activation deficits in PMD might be associated with inadequate resources for controlled semantic processing involved with successful verbal memory encoding (Sperling et al., 2003; Kirwan et al., 2008). Right insula deficits in PMD compared to NPMD might be associated with dysfunction of verbal working memory networks (Schulze et al., 2011).

Group comparisons of activation during retrieval showed that the PMD group had higher dorsolateral prefrontal and parietal cortex activations. As verbal memory retrieval networks include prefrontal and parietal regions (Spaniol et al., 2009), this finding might be interpreted as neural compensation for inefficient encoding. Similar findings of stronger prefrontal and parietal activation during retrieval in schizophrenia also have been interpreted as compensation for encoding deficits (Ragland et al., 2004). However, despite increased neural effort during retrieval the PMD group showed poor recognition accuracy. Despite shared prefrontal deficits in the PMD and NPMD groups during encoding, the NPMD group did not demonstrate retrieval deficits or recruit compensatory activation during retrieval.

Our results support the hypothesis that verbal memory deficits in PMD are associated with aberrant hippocampus and prefrontal activation during encoding. After accounting for poor recognition accuracy in PMD, higher activations associated with memory retrieval networks appear to be recruited, in PMD only, as compensation for encoding deficits. This interpretation is preliminary, however, as our blocked task design does not allow accurate isolation of successful versus unsuccessful encoding trials or correct versus incorrect recognition trials (e.g., too few incorrect trials are available). Therefore, we cannot conclusively determine that decreased prefrontal activation is detrimental to effective encoding or that increased prefrontal and parietal activation aids recognition accuracy. It is possible, instead, that observed abnormalities represent efficient encoding networks and ineffective retrieval mechanisms, which contribute to retrieval deficits in PMD. However, this explanation appears unlikely as studies have shown that increased depth of semantic

encoding and memory strength during retrieval have corresponded to increased activation in the prefrontal cortex (Otten et al., 2001; Kahn et al., 2004; Vilberg and Rugg, 2007).

Our study included only those subjects who achieved retrieval scores greater than chance, as we could not be certain whether extremely low scores could be attributed to noncompliance with task demands, failure of the response device, or neuropsychological deficits. Therefore, we may have excluded those PMD subjects who could not adequately engage encoding or retrieval networks due to task difficulty. Additional limitations to this analysis include medication exposure in PMD and NPMD groups. Particularly, the use of antipsychotic medication by most of the PMD subjects but none of the NPMD subjects confounds our comparisons of these groups and may account for some of the group differences reported here. However, we have not observed an effect of medications on cognitive performance (Schatzberg et al., 2000; Gomez et al., 2006, 2009) or fMRI activation (Greicius et al., 2007) in our subjects and this is consistent with the observations of others on antipsychotic versus drug-free status on fMRI of related functions in schizophrenia (Barch et al., 2001; Snitz et al., 2005; Yoon et al., 2008) or bipolar disorder (Phillips et al., 2008). Still, our results should be considered preliminary, and future studies would benefit from imaging subjects before they are placed on essential medications, or including larger samples that allow quantification of medication effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Main effect of group: activation clusters. Main effect of group results of 2-way group by task analysis of variance: two clusters were significant, including the sub-gyral right anterior cingulate and left parietal lobule. Extracted clusters were adjusted for recognition accuracy using unstandardized residuals and means plotted using bar graphs including ± 2 standard error. Blue bars represent means extracted from memory encoding task and green represent means extracted from the memory retrieval task. Statistical results are presented for each cluster in Table 3.

Fig. 2.

Interaction group by task: activation clusters. Interaction of group by task results of 2-way group by task analysis of variance: six of ten significant clusters were analyzed, including the right and left insula and hippocampus, left middle frontal gyrus, and right dorsolateral prefrontal cortex. Extracted clusters were adjusted for recognition accuracy using unstandardized residuals and means plotted using bar graphs including ± 2 standard error. Blue bars represent means extracted from memory encoding task and green represent means extracted from the memory retrieval task. Statistical results are presented for each cluster in Table 3.

Table 1

Demographic variables.

Descriptor mean (SD)	Psychotic major depression group (PMD) <i>N</i> =16	Non-psychotic major depression group (NPMD) <i>N</i> =15	Healthy control group (HC) <i>N</i> =16	ANOVA and posthoc <i>T</i> -tests ^a
Age	35.57 (11.70) range=18–54	35.78 (11.81) range=20–59	32.74 (13.55) range=18–57	$F(2,43)=0.283, p=0.753$
Education, years	16.15 (3.97) range=9–23 (<i>N</i> =13)	14.45 (1.50) range=12–16 (<i>N</i> =11)	15.46 (2.40) range=12–20 (<i>N</i> =13)	$F(2,33)=1.042, p=0.364$
Left handed	4 (<i>N</i> =13)	2	1	$c^b(1,44)=3.336, p=0.189$
WTAR predicted ^b	111.80 (12.72) (<i>N</i> =10)	100.18 (25.03) (<i>N</i> =11)	110.94 (8.98) (<i>N</i> =16)	$F(2,34)=1.818, p=0.178$
Hamilton depression rating scale	29.06 (4.12) range=21–37	24.53 (3.09) range=21–31	0.47 (0.52) range=0–1	$F(2,43)=457.2, p<0.001$ PMD>NPMD, *PMD>HC, *NPMD>HC, *
Brief psychiatry rating scale—positive symptom subscale score (–4)	8.06 (3.33) range=3–14	0.13 (0.35) range=0–1	0	$F(2,43)=88.06, p<0.001$ PMD>NPMD, *PMD>HC, *
Endogenomorphic scale	9.69 (1.88)	8.13 (1.40)	0	$F(2,43)=237.18, p<0.001$, PMD>HC, *NPMD>HC, *
Age at onset	25.11 (12.86) range=10–51 (<i>N</i> =9)	31.77 (11.89) range=17–51 (<i>N</i> =9)	N/A	$t(16)=1.224, p=0.285$
Gender distribution	8 F/8 M	8 F/7 M	7 F/9 M	$c^b(1,47)=0.296, p=0.863$
Current medication ^c	2 none; 4 anx; 7 AD; 9 AP; 1 MS (<i>N</i> =12)	8 none; 1 anx; 7 AD; 0 AP; 1 MS	N/A	AD use is similar but AP use in PMD group only
Comorbid diagnoses	6 none, 4 anxiety disorder ^d (<i>N</i> =10)	8 none, 7 anxiety disorder ^e	N/A	Similar; however, limited data available

^a Only significant posthoc *T*-test *p*-values presented.^b Wechsler test of reading (WTAR) estimate of premorbid full scale IQ.^c For medication; anx=anxiolytics; AD=antidepressant; AP=antipsychotic, MS=mood stabilizer.^d Anxiety disorders in the PMD group included 1 subject with panic disorder, 2 with agoraphobia, 1 with GAD, 2 with PTSD, 1 with anxiety NOS, 1 with specific phobia, 1 with social phobia.^e Anxiety disorders in the NPMD group included 1 subjects with OCD, 1 with agoraphobia, 1 with GAD, 2 with social phobia, 4 with specific phobia.* $p<0.001$.

Table 2

Task accuracy and reaction times.

Descriptor mean (SE)	Psychotic major depression group (PMD) <i>N</i> =16	Non-psychotic major depression group (NPMD) <i>N</i> =15	Healthy control group (HC) <i>N</i> =16	ANOVA results and posthoc <i>T</i> -tests ^a
<i>Encoding condition</i>				
Percent accuracy	89.40±12.77	94.40±8.40	93.34±6.51	<i>F</i> (2,43)=1.175, <i>p</i> =0.318
Response time for correct responses, ms	1238.44±237.41	1114.93±206.81	1131.20±153.19	<i>F</i> (2,43)=1.738, <i>p</i> =0.188
<i>Control condition</i>				
Percent accuracy	97.65±3.19	93.26±8.71	95.00±5.40	<i>F</i> (2,43)=2.026, <i>p</i> =0.144
Response time for correct responses, ms	586.09±202.38	589.68±192.36	578.18±150.87	<i>F</i> (2,43)=0.002, <i>p</i> =0.998
<i>Retrieval condition</i>				
Percent accuracy: recognized words	68.28±13.63	79.10±12.60	79.36±12.16	<i>F</i> (2,47)=3.852, <i>p</i> =0.029, HC>PMD <i>p</i> =0.02, NPMD>PMD <i>p</i> =0.03
Percent accuracy: novel words	83.59±14.76	79.79±12.98	77.74±14.47	<i>F</i> (2,43)=0.708, <i>p</i> =0.498
Correct response time: recognized words, ms	1195.89±215.92	1153.72±135.09	1089.12±139.67	<i>F</i> (2,43)=1.63, <i>p</i> =0.207
Correct response time: novel words, ms	1274.35±236.06	1183.48±132.59	1197.56±273.14	<i>F</i> (2,43)=0.753, <i>p</i> =0.477
False alarm rate	0.072±0.063	0.065±0.048	0.059±0.041	<i>F</i> (2,43)=0.277, <i>p</i> =0.759
Recognition discriminability (<i>d'</i>)	2.25±0.80	2.68±0.67	2.81±0.80	<i>F</i> (2,43)=2.418, <i>p</i> =0.101, HC>PMD <i>p</i> =0.041
<i>Control condition</i>				
Percent accuracy	93.77±9.28	96.39±6.72	93.25±10.97	<i>F</i> (2,43)=0.512, <i>p</i> =0.603
Response time for correct responses, ms	533.47±180.73	538.22±138.09	536.50±125.94	<i>F</i> (2,43)=0.004, <i>p</i> =0.996

^aOnly significant posthoc *T*-test *p*-values presented.

Table 3

Significant clusters of activation from the main effect of group for encoding minus control and retrieval minus control contrasts.

Neuroanatomy	BA	Cluster size	Talairach coordinates	F value	Post-hoc <i>T</i> -test*
ROI analysis: main effect of group					
Left parietal lobule	40	24	-46, -33, 38	8.80	Encoding; no significance, retrieval; PMD>HC, $p<0.001$, PMD>NPMD, $p=0.013$
Sub-gyral, right anterior cingulate	32	19	22, 39, 2	8.93	Encoding; HC>PMD, $p=0.001$, HC>NPMD, $p=0.010$, retrieval; HC>PMD, $p=0.009$, HC>NPMD, $p=0.003$
ROI analysis: interaction of group×task					
Right insula	13	23	42, 2, 2	9.02	Encoding; NPMD>PMD, $p=0.003$, HC>PMD, $p=0.016$, retrieval; no significance
Left insula	13	93	-36, 1, 20	12.39	Encoding; HC>PMD, $p=0.018$, HC>NPMD, $p=0.044$, retrieval; no significance
Right hippocampus		19	24, -7, -18	9.93	Encoding; HC>PMD, $p=0.007$, retrieval; no significance
Left hippocampus		26	-20, -11, -18	8.98	Encoding; HC>PMD, $p=0.027$, HC>NPMD, $p=0.009$, retrieval; no significance
Left middle frontal gyrus	8	132	-20, 19, 38	11.53	Encoding; HC>PMD, $p=0.001$, HC>NPMD, $p=0.038$, retrieval; PMD>NPMD, $p=0.032$
Right dorsolateral prefrontal cortex	10	49	26, 59, 14	8.98	Encoding; no significance, retrieval; PMD>HC, $p=0.031$
Left mid-cingulate gyrus	31	163	-18, -22, 34	10.22	
Left mid-cingulate gyrus	24	71	-8, 6, 33	12.30	
Right precentral gyrus	44	11	63, 8, 11	8.54	
Right superior frontal gyrus	8	14	22, 18, 41	8.31	

* Cluster significance within two 2-group *t*-tests; clusters from main effect of group defined at $p=0.025$, clusters from interaction of group×task defined at $p=0.0083$.