



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 man-made.” 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.

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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 healthy control (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

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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

The initial sample comprised 24 subjects with PMD, 19 subjects with NPMD, and 21 HC subjects. After screening for exclusionary criteria (see below), 16 subjects with PMD, 15 subjects with NPMD, and 16 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 Psychiatric 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

Table 1
Demographic variables.

Descriptor mean (SD)	Psychotic major depression group (PMD) N=16	Non-psychotic major depression group (NPMD) N=15	Healthy control group (HC) N=16	ANOVA and post hoc T-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 (N=13)	14.45 (1.50) range=12–16 (N=11)	15.46 (2.40) range=12–20 (N=13)	$F(2,33)=1.042, p=0.364$
Left handed	4 (N=13)	2	1	$\chi^2(1,44)=3.336, p=0.189$
WTAR predicted ^b	111.80 (12.72) (N=10)	100.18 (25.03) (N=11)	110.94 (8.98) (N=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 Psychiatric 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 (N=9)	31.77 (11.89) range=17–51 (N=9)	N/A	$t(16)=1.224, p=0.285$
Gender distribution	8 F/8 M	8 F/7 M	7 F/9 M	$\chi^2(1,47)=0.296, p=0.863$
Current medication ^c	2 none; 4 anx; 7 AD; 9 AP; 1 MS (N=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 (N=10)	8 none, 7 anxiety disorder ^e	N/A	Similar; however, limited data available

^a Only significant post hoc 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.

* $p < 0.001$.

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