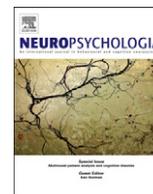




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Association between subcortical volumes and verbal memory in unmedicated depressed patients and healthy controls

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ABSTRACT

Research has shown poor performance on verbal memory tasks in patients with major depressive disorder relative to healthy controls, as well as structural abnormalities in the subcortical structures that form the limbic-cortical-striatal-pallidal-thalamic circuitry. Few studies, however, have attempted to link the impairments in learning and memory in depression with these structural abnormalities, and of those which have done so, most have included patients medicated with psychotropic agents likely to influence cognitive performance. This study thus examines the relationship between subcortical structural abnormalities and verbal memory using the California Verbal Learning Test (CVLT) in unmedicated depressed patients. A T1 weighted magnetic resonance imaging scan and the CVLT were obtained on 45 subjects with major depressive disorder and 44 healthy controls. Using the FMRIB's Integrated Registration and Segmentation Tool (FIRST) volumes of selected subcortical structures were segmented and correlated with CVLT performance. Depressed participants showed significantly smaller right thalamus and right hippocampus volumes than healthy controls. Depressed participants also showed impaired performance on global verbal learning ability, and appeared to depend upon an inferior memory strategy (serial clustering). Measures of serial clustering were correlated significantly with right hippocampal volumes in depressed participants. Our findings indicate that depressed participants and healthy controls differ in the memory strategies they employ, and that while depressed participants had a smaller hippocampal volume, there was a positive correlation between volume and use of an inferior memory strategy. This suggests that larger hippocampal volume is related to better memory recall in depression, but specifically with regard to utilizing an inferior memory strategy.

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1. Introduction

A diagnosis of major depressive disorder includes clinical features of cognitive dysfunction such as “diminished ability to think or concentrate, or indecisiveness,” (APA, 2000). Neuropsychological studies that evaluate the cognitive features of depression have identified deficits in information processing, attention, memory, and executive functioning (Reppermund, Ising et al., 2009). Memory dysfunction is apparent in declarative memory (Campbell & MacQueen, 2006), with the largest effects in the domains of encoding and retrieval of episodic memory (Zakzanis, Leach et al., 1998). Studies of episodic memory deficits in depression have examined both autobiographical memory and explicit memory. With regard to autobiographical memory,

depressed participants tend to be over-general in their recall of events triggered by a cue word (Williams et al., 2007; Young et al., in press). Most examinations of explicit memory in depression have focused on verbal memory. For example, in studies comparing depressives and controls for their performance on the California Verbal Learning Test (CVLT; (Delis et al., 2000), an assessment of verbal memory, retention, and retrieval, the depressed participants were slower to acquire new information, and recalled fewer target words. In contrast, memory retention and recognition memory appear relatively preserved in major depression (Otto, Bruder et al., 1994).

Verbal memory deficits observed in patients with depression conceivably may be mediated by the abnormalities in brain structure and function that have been identified in neuroimaging and neuropathological studies of major depression (Sheline, Wang et al., 1996; Gold, Drevets et al., 2002). Such abnormalities commonly have been reported to involve subcortical structures such as the amygdala, hippocampus, striatum and thalamus (Bremner, 2005; Amico, Meisenzahl et al., 2011). These structures, along with the prefrontal and temporal cortices, form the limbic-cortical-striatal-pallidal-thalamic circuit that plays a role in

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supporting affective states, episodic memory, and other types of cognitive processing (Sheline, 2000; Bielau, Trubner et al., 2005; Kim, Hamilton et al., 2008).

The hippocampus is critically involved in learning and memory, particularly in consolidation of short-term into long-term explicit memory (Squire, 1992; Schacter, Alpert, Savage, Rauch, & Alpert, 1996; Eichenbaum, 1997; Nadel, Ryan, Hayes, Gilboa, & Moscovitch, 2003). The hippocampus has been linked with performance on tasks of delayed recall (Geuze, Vermetten et al., 2005) and damage to the hippocampus gives rise to explicit memory deficits (Sapolsky, 2000). In addition, lesion (Serra-Grabulosa, Junque et al., 2005) and resection (Hermann, Wyler et al., 1994) studies have shown that hippocampal damage impairs performance on recall measures of the CVLT (Hermann et al., 1994; Serra-Grabulosa et al., 2005).

Structural magnetic resonance imaging (MRI) studies show smaller hippocampal volumes in major depression (Videbech & Ravnkilde, 2004; Clark, Chamberlain et al., 2009; Ystad, Lundervold et al., 2009), although this finding remains inconsistent in the literature (Ashtari, Greenwald et al., 1999; Vythilingam, Vermetten et al., 2004). Although in some cases differences in the results across studies may be due to methodological issues such as the use of lower resolution MRI techniques and differences in segmentation procedures, in other cases they may reflect the biological heterogeneity extant within the population encompassed by the major depressive disorder criteria (Sapolsky, 2000; Sheline, 2000). For example, theories exist regarding the relationship between cortisol hypersecretion, hippocampal abnormalities and verbal memory deficits and the neurobiology of depression. The prevailing hypothesis is that hippocampal neuronal damage may be caused by excess secretion of cortisol, particularly in the context of prolonged stress, and/or glutamatergic excitotoxicity (for review see Gold, Drevets et al., 2002), although the relationship between these pathological constructs has been only partly elucidated.

Other subcortical structures implicated in the pathophysiology of major depressive disorder, such as the basal ganglia, play roles in implicit learning and memory, and in working memory (Packard & Knowlton, 2002; Ring & Serra-Mestres, 2002; Graybiel, 2005). Also, the basal ganglia have also been implicated in mediating certain memory strategies, such as route recognition, via their limbic-cortical-striatal-pallidal-thalamic circuit interactions (Voerman et al., 2004). The basal ganglia have been implicated in depression due to the comorbidity of depression with neurodegenerative disorders that involve the basal ganglia, such as Parkinson's disease and Huntington's disease (Husain, McDonald et al., 1991; Krishnan, McDonald et al., 1992; Ring & Serra-Mestres, 2002). Neuroimaging studies have shown smaller putamen and caudate volumes (Husain et al., 1991; Krishnan et al., 1992), while postmortem studies have shown smaller putamen, pallidum, and accumbens volumes in depressed participants compared to healthy controls (Baumann, Danos et al., 1999). In addition, lesion studies link the caudate nucleus and the putamen with depression, and patients with lesions in the caudate and putamen tend to have both higher frequency and higher severity of depression (Starkstein, Robinson et al., 1988).

The thalamus also has been implicated in the pathophysiology of major depression in neuroimaging studies (e.g., (Drevets, 1998; Kim et al., 2008). Volumetric MRI (Kim et al., 2008) and post-mortem (Bielau et al., 2005) studies identified smaller thalamic volumes in depressed participants compared to healthy controls. In addition, patients with thalamic lesions tend to have memory difficulties that include retrieval and encoding deficits (Van der Werf, Witter et al., 2000).

In summary, while both verbal memory deficits and subcortical abnormalities have been demonstrated in patients suffering from major depression, the relationship between subcortical

volume and verbal memory remains unclear. Further insight into this relationship could facilitate our understanding of the pathophysiology underlying mood disorders, and potentially may contribute to improved diagnosis and treatment for major depressive disorder. We predicted that volumes of subcortical regions involved in the limbic-cortical-striatal-pallidal-thalamic circuit that support verbal memory processing would be reduced in depressed participants as compared to healthy controls. Moreover, we expected that volumes in areas showing group differences would correlate with indices of verbal memory dysfunction.

2. Methods and materials

2.1. Participants

Forty-five currently unmedicated (for at least 2 weeks, and at least 4 weeks for those treated with fluoxetine) patients were enrolled in this study after meeting Diagnostic and Statistical Manual for Mental Disorders (4th ed., text rev.; DSM-IV-TR; APA, 2000) criteria for major depressive disorder without psychotic features (18 males, 27 females; mean age = 36 ± 10 ; range 19–56 years). Mental health status was determined by the structured clinical interview for the DSM-IV-TR (SCID) (First, Spitzer, Gibbon, & Williams, 1995) administered by trained research nurses with at least 80 interrater reliability and confirmed via an unstructured interview with a psychiatrist. Healthy controls (20 males, 24 females; age = 33 ± 10 ; range 20–57 years) had no current lifetime or history of a psychiatric disorder (also ascertained via the SCID and an unstructured interview with a psychiatrist), and did not have a first-degree relative with a mood or anxiety disorder. Exclusion criteria for all participants as determined by medical history, physical examination and laboratory testing included significant medical or neurological disorders, head injury with loss of consciousness, pregnancy, general MRI exclusions, meeting DSM-IV-TR (APA, 2000) criteria for substance abuse within the preceding 90 day, or a positive urine toxicology screen. All participants were evaluated at the National Institute of Mental Health outpatient clinic. Written informed consent was obtained from all participants, and all data were collected as approved by the National Institutes of Health Combined Neuroscience Institutional Review Board.

2.2. Verbal memory task

The California Verbal Learning Test (CVLT; (Delis et al., 2000)) was used to assess verbal learning, retention, and retrieval. The CVLT is a retrieval-trial, list-learning test, with two 16-item lists. List A, which consists of four semantic categories, is read to the participants, and is presented so that no two words from the same category occur in sequence. Participants are not informed of the semantic structure. The list is presented for five trials, after each of which the participant is asked to recall as many of the words as possible (immediate free recall). A total free recall score is computed by adding trials one through five. Immediately after trial 5, List B is presented (again this list is comprised of four semantic categories, two of which overlap with List A), and participants were asked to recall these words once. Following this single trial with List B, the participants are asked to recall List A once with no prompt (short delay free recall), and then a second time when prompted with semantic category (short delay cued recall). Following a 20 min delay, participants are asked to recall as many words from List A as possible, first via free recall (long delay free recall) then via cued recall (long delay cued recall). Finally, a List A recognition trial included the presentation of a word list comprised of List A words, List B words and novel words.

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