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Sources of declarative memory impairment in bipolar disorder: Mnemonic processes and clinical features

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Abstract

Background: There is mounting evidence that declarative memory processes are impaired in patients with bipolar disorder. However, predictors of the observed impairment are not well understood. This study seeks to: (i) better characterize the nature of declarative memory impairment in bipolar disorder, and (ii) determine the relationship between clinical variables and memory function in bipolar disorder.
Methods: 49 adult patients with bipolar disorder in varying mood states and 38 demographically matched healthy participants completed a comprehensive neurocognitive battery assessing general cognitive functioning, processing speed, and declarative memory. The California verbal learning test was used to characterize learning and memory functions.
Results: Although patients with bipolar disorder utilized a similar semantic clustering strategy to healthy controls, they recalled and recognized significantly fewer words than controls, suggesting impaired encoding of verbal information. In contrast, lack of rapid forgetting suggests relative absence of a storage deficit in bipolar patients. While severity of mood symptomatology and illness duration were not associated with task performance, gender and family history significantly affected memory function.
Conclusions: Results suggest that declarative memory impairments in bipolar patients: (1) are consistent with deficits in learning, but do not appear to be related to different organizational strategies during learning, and (2) do not appear to be secondary to clinical state, but rather may be associated with the underlying pathophysiology of the illness.

Keywords: Bipolar disorder; Clinical state; Declarative memory; Cognition; Gender

1. Introduction

Verbal declarative memory impairments are among the most consistently reported cognitive difficulties in clinical remitted patients with bipolar disorder (Cavanagh et al., 2002; Clark et al., 2001; Deckersbach et al.,

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2004; van Gorp et al., 1999). Given that these deficits have also been observed in unaffected relatives of patients with bipolar illness (Ferrier et al., 2004; Keri et al., 2001), declarative memory dysfunction may represent a vulnerability marker for bipolarity. However, predictors of the observed impairment are not well understood.

Declarative memory, or the explicit recall of previously learned information, relies on the ability to adequately encode, store, and retrieve verbal information (Gabrieli et al., 1998; Kapur et al., 1996). Encoding involves converting a perceived event into a lasting neurophysiological trace (Kapur et al., 1996), while retrieval refers to the process that reactivates a stored representation, leading to an explicit 'memory' of the event (Deckersbach et al., 2004). These cognitive functions (encoding, storage, and retrieval) are thought to be subserved by distinct brain regions. In particular, medial temporal regions are involved in both encoding and retrieval of verbal information, while strategic or executive aspects of memory rely on prefrontal cortical function (Cabeza and Nyberg, 2000; Lepage et al., 1998).

Declarative memory deficits are of increasing interest in bipolar disorder because of their potential association with neurophysiologic and neuroanatomic abnormalities in frontal and temporal brain regions, which have been implicated in the pathophysiology of the illness (Deckersbach et al., 2004; Soares, 2003). In particular, there is increasing evidence for prefrontal cortical pathology in bipolar disorder; several studies have found volumetric reduction in subregions of the prefrontal cortex (Drevets et al., 1997; Sax et al., 1999; Hirayasu et al., 1999; Lopez-Larson et al., 2002), corroborating postmortem findings of reduced density of neuronal and glial cells in the dorsolateral prefrontal cortex (Rajkowska et al., 2001), and decreased clustering of neurons and decreased somal size in anterior cingulate cortex (Chana et al., 2003). However, evidence for temporal lobe pathology in bipolar disorder is less consistent, with various studies reporting volumetric increases (Harvey et al., 1994), decreases (Hauser et al., 1989), and no differences, as compared to normal controls (Johnstone et al., 1989; Altshuler et al., 2000). Similarly, the majority of studies have not reported structural abnormalities of the hippocampus in patients with bipolar disorder (see Monkul et al., 2003 for a review). Nevertheless, postmortem investigations have reported decreased density of non-pyramidal neurons in region CA2 of the hippocampus (Benes et al., 1998), as well as decreased hippocampal expression of GABA-synthesizing messenger RNA (Heckers et al., 2002) suggesting that more subtle hippocampal pathology may be present in bipolar disorder, in the absence of global volume deficits.

In addition, these cognitive deficits are associated with persistent psychosocial difficulties, even in asymptomatic patients with bipolar disorder (Atre-Vaidya et al., 1998; Ferrier et al., 1999; Scott, 1995), raising the possibility that cognitive problems contribute significantly to lack of full functional recovery from affective episodes.

Despite the potential importance of memory deficits for the outcome of bipolar patients (Dickerson et al., 2003), there is debate about the nature of these impairments. While there is some evidence that poor memory performance is secondary to strategic or organizational dysfunction rather than impaired memory processes per se (Deckersbach et al., 2004), other studies suggest that memory deficits in patients with bipolar disorder may be secondary to clinical symptomatology (Kessing, 1998). Sweeney et al. (2000) identified widely distributed cognitive deficits in mixed/manic bipolar patients, while depressed bipolar and unipolar patients demonstrated impairments only on an episodic memory test, suggesting a more selective dysfunction in mesial temporal lobe function during depressive episodes. Yet, in one of the larger studies of memory functioning in bipolar disorder, Martinez-Aran et al. (2004) found little relationship between clinical state and neurocognitive deficits, suggesting that this relationship may be mediated by other factors. In particular, memory performance may be adversely affected by severity of illness, as measured by number of hospitalizations, number and duration of manic and/or depressive episodes, and age at onset (Cavanagh et al., 2002; Clark et al., 2002; Kessing, 1998; Tham et al., 1997), although others have found no relationship (Atre-Vaidya et al., 1998; Verdoux and Liraud, 2000). In addition, gender may modulate the severity of cognitive deficits in bipolar disorder, with male patients demonstrating poorer neurocognitive performance (Sweeney et al., 2000).

This disparity in findings is problematic and reflects the substantial variability in study design and methodology, as well as patient characteristics, that is common in much of the research to date (Burt et al., 1995). For instance, only recently have investigators made efforts to distinguish bipolar from unipolar affective illness, and to carefully assess mood state at time of testing (Bearden et al., 2001).

More recent studies that have assessed bipolar patients in the euthymic phase of illness using declarative memory tasks have identified significant verbal learning and memory impairments in the absence of prominent mood symptoms (e.g., Clark et al., 2002; Cavanagh et al., 2002; van Gorp et al., 1999, 1998; Altshuler et al., 2004). However, most have reported only overall scores or basic performance indices; to our knowledge only one study specifically attempted to delineate the underlying cognitive processes that may be disrupted (Deckersbach et al., 2004). In addition, while such studies have substantially advanced our understanding of trait aspects of cognitive function in bipolar disorder, it is not clear whether euthymic bipolar patients