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Brief Communication

Impaired sustained attention and executive dysfunction: Bipolar disorder versus depression-specific markers of affective disorders☆

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ABSTRACT

Objective: To identify neurocognitive measures that could be used as objective markers of bipolar disorder.
Methods: We examined executive function, sustained attention and short-term memory as neurocognitive domains in 18 participants with bipolar disorder in euthymic state (Beuth), 14 in depressed state (Bdep), 20 with unipolar depression (Udep) and 28 healthy control participants (HC). We conducted four-group comparisons followed by relevant post hoc analyses.
Results: Udep and Bdep, but not Beuth showed impaired executive function ($p = 0.045$ and $p = 0.046$, respectively). Both Bdep and Beuth, but not Udep, showed impaired sustained attention ($p = 0.001$ and $p = 0.045$, respectively). The four groups did not differ significantly on short-term memory. Impaired sustained attention and executive dysfunction were not associated with depression severity, duration of illness and age of illness onset. Only a small number of abnormal neurocognitive measures were associated with medication in Bdep and Beuth.
Conclusion: Impaired sustained attention appears specific to bipolar disorder and present in both Beuth and Bdep; it may represent an objective marker of bipolar disorder. Executive dysfunction by contrast, appears to be present in Udep and Bdep and likely represents a marker of depression.

Bipolar disorder is one of the most debilitating of all illnesses (Murray & Lopez, 1996). It is associated with poor prognosis and high mortality rate (Baldessarini & Tondo, 2003). One reason for the poor prognosis is the frequent misdiagnosis of the disorder (Bowden, 2001) especially in patients presenting with depression and no clear history of mania which results in inadequate treatment (Bowden, 2001; Ghaemi, Ko, & Goodwin, 2002; Lish, Dime-Meenan, Whybrow, Price, & Hirschfeld, 1994). Increased accuracy in diagnosing bipolar disorder can be best achieved by the identification of objective biological markers, reflecting underlying neural mechanisms that underlie core clinical features of the disorder, that are both persistent (i.e. present across different mood states) and specific to bipolar disorder (i.e. not present in unipolar depression). Neurocognitive task performance measures are valuable and easily obtainable indirect measures of function within neural systems supporting different domains of cognition. Examination of abnormalities in performance on specific neurocognitive tasks in individuals with bipolar disorder and those with unipolar depression can therefore provide valuable insights into neural mechanisms that differ between these two illnesses and that can ultimately provide objective biological markers needed to help improve diagnostic accuracy for bipolar disorder and unipolar depression. We next review the literature that has provided some evidence for persistent patterns of neurocognitive task performance abnormalities in bipolar disorder, and for distinguishable patterns of abnormalities on these measures in bipolar and unipolar depressions, in domains of cognition that are relevant to understanding neural mechanisms underlying core symptoms of these illnesses.

Examples of domains of cognition relevant to understanding neural mechanisms of bipolar disorder and unipolar depression include memory, attention, and executive function, a term used interchangeably with cognitive control, that refers to higher-level cognitive functions involved in the control and direction of mem-

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ory and attention in order to flexibly organize behavior and engage in forward planning (Clark et al., 2009; Stuss & Levine, 2002). These domains are all key component subprocesses of emotion regulation, a core abnormality in both bipolar disorder and unipolar depression (Phillips, Ladouceur, & Drevets, 2008). There is strong evidence, for example, that bipolar disorder is associated with neurocognitive deficits including impaired executive function, sustained attention and short-term memory during acute phases of the illness and remission (Bearden, Hoffman, & Cannon, 2001). Several studies also examined the extent to which impairments in executive function, sustained attention and short-term memory may represent objective markers of bipolar disorder that persist across different mood states (Clark, Iversen, & Goodwin, 2002; Clark, Kempton, Scarna, Grasby, & Goodwin, 2005; Ferrier, Stanton, Kelly, & Scott, 1999; Liu et al., 2002; Mur, Portella, Martinez-Aran, Pifarre, & Vieta, 2007; Rubinsztein, Michael, Paykel, & Sahakian, 2000). Other studies examined the extent to which impairments in these different neurocognitive domains were also present in unipolar depression (Borkowska & Rybakowski, 2001; Van der Meere, Borger, & van Os, 2007; Wolfe, Granholm, Butters, Saunders, & Janowsky, 1987). The above studies specifically reported impaired executive function in bipolar depression, which exists to a greater extent than in unipolar depression (Borkowska & Rybakowski, 2001), although at least one study indicated no difference between unipolar and bipolar depressions on executive function (Gruber, Rathgeber, Braunig, & Gauggel, 2007). A number of studies and a recent meta-analyses reported that impaired executive function persists in remission in bipolar disorder (Ferrier et al., 1999; Mur et al., 2007; Rubinsztein et al., 2000), and is present in first degree relatives of patients with bipolar disorder (Clark, Sarna, & Goodwin, 2005). The persistence of impaired executive function during remission in bipolar disorder was not confirmed in all studies, however (Clark et al., 2002). Findings indicate impaired executive function in unipolar depression (Elliott et al., 1996; Merriam, Thase, Haas, Keshavan, & Sweeney, 1999) that is independent of medication status (Taylor Tavares et al., 2007). The degree of executive impairment may be specific to symptom dimensions such as apathy (Feil, Razani, Boone, & Lesser, 2003), and may be independent of symptom severity (Porter, Gallagher, Thompson, & Young, 2003). Impaired executive function improves significantly with remission in patients with unipolar depression, although residual deficits may remain to some degree (Clark, Sarna, et al., 2005).

Studies have also reported impaired sustained attention in bipolar disorder during mania, remission and in first degree relatives of patients with bipolar disorder (Clark et al., 2002; Clark, Kempton, et al., 2005; Liu et al., 2002). Impairment during remission, appears to be medication-independent and manifests as decreased target sensitivity on a sustained attention task whereas impairment during mania manifests as increased false responding and perseveration and is partly explained by the impact of medications (Bora et al., 2006). A few studies that examined sustained attention in bipolar depression indicate impairments in this domain in medicated bipolar depressed patients (Holmes et al., 2008). Findings in unipolar depression, by contrast, indicate possible impairment in this domain (Van der Meere et al., 2007), which may subside in partially and completely remitted patients (Clark, Kempton, et al., 2005; Liu et al., 2002).

There is evidence that short-term memory is disrupted in bipolar depression (Sweeney, Kmiec, & Kupfer, 2000), potentially more than in unipolar depression (Wolfe et al., 1987). This may be state-specific (Ferrier et al., 1999), although some studies detected persisting short-term memory impairments in remission (Rubinsztein et al., 2000). Short-term memory dysfunction increases with illness duration and number of mood episodes (Bearden et al., 2006), and may predict functional outcome (Martinez-Aran et al., 2004). Consolidation of short-term memory into long-term storage is impaired in unipolar depression (Wolfe et al., 1987). This impairment may subside during remission (Clark, Sarna, et al., 2005), increase with illness chronicity and correlate with the total length of time spent in a depressed state in unipolar depression (Gorwood, Corruble, Falissard, & Goodwin, 2008). This deficit may be related to the progressive hippocampal degeneration in unipolar depression (MacQueen et al., 2003).

A major problem with these previous studies is that they were not specifically designed to directly compare different groups of bipolar and unipolar depressed individuals, in order to examine the extent to which impairments in these neurocognitive domains represented specific and persistent objective markers of bipolar disorder, and therefore did not include both bipolar disorder patients in different mood states and depressed patients with unipolar depression (Clark & Sahakian, 2008). An additional problem with these studies is that they employed different tasks to measure function within these cognitive domains, which makes it extremely difficult to directly compare findings among them. We therefore wished to determine the extent to which dysfunction in these three different neurocognitive domains were evident in different mood states in bipolar disorder, and whether they were present in unipolar depression. We employed well-validated computerized tests of the three cognitive domains that were administered to four groups of participants: bipolar euthymic (Beuth), bipolar depressed (Bdep), unipolar depressed (Udep) and healthy controls (HC).

Our specific aims were twofold:

1. To determine the extent to which abnormalities in these three cognitive domains were persistent markers of bipolar disorder. We hypothesized that Beuth would show impaired sustained attention relative to HC, while Bdep would show impaired executive function relative to HC. Existing data did not allow us to specify whether Bdep would show similar level of impairment on sustained attention as Beuth, or whether impaired executive function would characterize Bdep but not Beuth.
2. To determine the extent to which abnormalities in any of our three cognitive domains distinguished bipolar from unipolar depression. We hypothesized that both Bdep and Udep would show impaired executive function and short-term memory relative to HC. Existing data did not allow us to specify whether impaired sustained attention would characterize Bdep but not Udep.

1. Methods

1.1. Participants

The study protocol was approved by the University of Pittsburgh Institutional Review Board. 32 outpatients meeting criteria for bipolar disorder type I according to DSM-IV and diagnosed using the Structured Clinical Interview for DSM-IV, Research Version participated in the study. 18 participants were in remission and euthymic (Beuth) at the time of testing with a Young Mania Rating Scale (YMRS) score $\leq$10 and a 25-item Hamilton Depression Rating Scale (HDRS-25) score $\leq$7, 14 participants were in depressed episode (Bdep; HDRS-25 $\geq$17). All participants had experienced at least two episodes of depression or mania in the last 4 years. In addition, 20 patients with recurrent unipolar depression (Udep), currently in depressed episode (HDRS-25 >17) and 28 healthy control participants (HC) with no previous psychiatric history or psychiatric history in first and second degree relatives were enrolled in the study. The groups were age, gender ratio and IQ-matched (Table 1). A record of participants' medications from the day of testing or up to 30 days prior was used; this information was missing in 10 participants (4 Bdep, 3 Beuth and 3 MDD). Exclusion criteria included a history of head injury, neurological disorder (cardiovascular accident, epilepsy, dementia, developmental disorder, loss of consciousness for more than 10 min), cognitive impairment (score <24 on Mini-Mental State Examination) (Folstein, Folstein, & McHugh, 1975), premorbid IQ estimate <85 (National Adult Reading Test), (Nelson & Willison, 1991) current alcohol and illicit substance abuse (determined by saliva and urine screen) and Axis-II borderline personality disorder. Additional exclusion criteria for HC included history of alcohol