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Research report

Differential abnormalities of functional connectivity of the amygdala and hippocampus in unipolar and bipolar affective disorders

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ABSTRACT

Objective: The amygdala and hippocampus – two structures intimately associated with mood and cognition – have been reported to exhibit altered neural activity or volume in affective disorders. We hypothesized the amygdala and hippocampus would show altered and differential patterns of connectivity in patients with bipolar (BPs) and unipolar (UPs) disorder compared to healthy volunteers.
Method: Thirty BPs, 34 UPs, and 66 healthy volunteers were imaged using F-18-fluorodeoxyglucose and positron emission tomography while performing an auditory continuous performance task (CPT). Normalized mean activity of the amygdala and hippocampus was correlated with the rest of the brain.
Results: In BPs, the amygdalae displayed exaggerated positive metabolic correlations with prefrontal and ventral striatal areas, while the hippocampus showed a paucity of normal inter-relations compared to controls. In contrast, in UPs the amygdala was significantly negatively correlated with prefrontal and anterior cingulate cortex, while the hippocampus was significantly more positively correlated to these same prefrontal areas.
Conclusions: During a simple cognitive task, the functional connectivity of the amygdala and hippocampus, regions usually associated with emotion and memory regulation, was substantially different in affective illness compared to healthy controls whether or not there were baseline abnormalities in these areas. These striking differences in functional connectivity of amygdala and hippocampus should be further explored in ill and well states and using more specific emotion and cognitive evocative tasks.
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1. Introduction

The amygdala and hippocampus are considered critical structures contributing to the dysregulation of emotional and cognitive functions, respectively, in bipolar (BP) and unipolar (UP) affective disorders. Each structure has been extensively studied and linked mechanistically to the symptomatic aspects of BP and UP disorders (Price and Drevets, 2012). Thus, the careful dissection of type of dysfunction or dysregulation of these structures would add considerably to the understanding of the pathophysiological processes underlying these two disorders. However, functional and structural neuroimaging findings supporting this belief have been variable (see reviews Strakowski et al., 2005; Drevets et al., 2008; Cerullo et al., 2009), so that the precise nature of these abnormalities and their consequences remain to be established. Furthermore, the emotional and cognitive deficits patients experience could be related not only to altered levels of activity within each region, but also to abnormal interregional relationships of these two critical regions with other brain areas.

Affective instability typifies bipolar illness where mood swings from depression to mania can cycle within months, days or even hours (Goldberg et al., 2009). Unipolar illness, on the other hand, is mainly characterized by low mood, anhedonia, and a host of vegetative disturbances, and is distinguished from bipolar disorder by the lack of manic episodes. Amygdalar and hippocampal dysfunction is thought to play a major role in these symptoms, often

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figuring predominately in models of affective disorders (Krishnan and Nestler, 2010; Price and Drevets, 2010; Strakowski et al., 2005).

Evidence of amygdala dysfunction in bipolar illness comes from neuroimaging studies. For example, increased baseline activity can occur in the depressed state (Drevets et al., 2002; Ketter et al., 2001) and in mania (Altshuler et al., 2005) compared to controls, and may normalize with euthymia (Ketter et al., 2001). When bringing the amygdala on-line with emotion tasks, increased activity has been observed in children (Chang et al., 2005; Leibenluft and Rich, 2008) and adults (Yurgelun-Todd et al., 2000) with bipolar disorder. It is unclear how these differences in activity relate to abnormalities in amygdalar volumes in bipolar illness that appear to vary across the life span (see review, Konarski et al., 2008; Sheline, 2003, as many investigators may not apply volume correction.

Similarly in unipolar depression, increased amygalar activity has been reported at rest (Drevets, 2000, 2003; Nofzinger et al., 1999; Siegle et al., 2002), during REM sleep (Ho et al., 1996), with sadness induction (Surguladze et al., 2005), and when viewing fearful or smiling faces (Sheline et al., 2001), or aversive (Heinz et al., 2005) or negative (Anand et al., 2005) pictures. However, decreased amygdala activity was also shown at rest (Anand et al., 2005) or during continuous performance task (CPT; Kimbrell et al., 2002) in UPs compared to controls.

Pessoa (2008) argues that emotion is not solely parceled into the limbic system and affective regions, but also involves functions in the cognitive domain, specifically to monitor potential salient stimuli. Thus, in addition to the emotion dysregulation, impairment in the cognitive domain also occurs in mood disorders including abnormalities of verbal and spatial memory, facial emotion recognition, and the inability to concentrate and maintain attention (Sheline, 2003). Attention deficits may also be a trait marker of mood disorders (Najt et al., 2005).

Consistent with this view, amygdalar activity is elevated during sustained attention in bipolar mania (Fleck et al., 2010). Moreover, normal amygdala activity is suppressed during cognitive engagement (Pessoa, 2005). Attention and executive functioning, which depend on these memory skills, may be compromised with greater illness severity (Altshuler et al., 2008b; McClintock et al., 2010); however, deficits persist in euthymia (Bearden et al., 2010). Yet, hippocampal activity in BPs (Bauer et al., 2005; Ketter et al., 2001; Chen and Desmond, 2005) is not consistently abnormal; metabolic activity has been reported as increased (Bauer et al., 2005; Ketter et al., 2001, no change (Drevets et al., 2002), and may differ across mood states with higher activity in mania compared to depression (Chen and Desmond, 2005). In contrast, hippocampal activity in UPs is often reported as abnormal, but there are discrepancies in the direction of change compared to controls.

While there are no consistent abnormalities in hippocampal volumes in biplar illness (Sheline, 2003), a large and highly consistent literature indicates that UPs have reduced hippocampal volume (Sheline et al., 1996; Sheline, 2003; Campbell et al., 2004; Videbech and Ravnkilde, 2004). Reports of amygdala volumes are variable (Sheline et al., 1998; Lange and Irle, 2004; Hastings et al., 2004; Rosso et al., 2005). Several investigators describe the left amygdala and right hippocampus were larger than their contralateral homologous structures (Bremner et al., 2000; Frodl et al., 2002, 2004; Mervaala et al., 2000). Thus, laterality may be important factor in unipolar illness.

These inconsistencies in discrete regional amygdalar and hippocampal structure and function in mood disorders suggest that other factors may contribute to these discrepancies. Questions remain as to how the functional significance of amygdala and hippocampal activity and volume changes relate to the other common findings in the affective disorders, such as decreased activity in prefrontal lobe areas (see reviews, Drevets et al., 2008; Strakowski et al., 2005).

One possible explanation is that the absolute or relative regional activity in the amygdala and hippocampus is only one aspect of dysfunction, and the functional relationships between these two key limbic regions and the regions to which they connect may explain the dysfunction these patients experience. For instance, initial studies reported increased functional connectivity of the amygdala in BPs and UPs compared to controls during emotive tasks (Irwin et al., 2004; Matthews et al., 2008; Yoshimura et al., 2010; Versace et al., 2008) and decreased during rest (Anand et al., 2005, 2009).

Using the methods of Horwitz et al. (1990,1991), we sought to examine the functional relationships of the amygdala and hippocampus during a simple cognitive task, where performance differences could be eliminated, and at the same time elucidate mechanisms of attention in a low-stress task. This paradigm may provide an ecologically sound paradigm where the simple cognitive activity leaves the opportunity of emotion to intrude in these emotionally labile patients, possibly mimicking everyday experiences.

We previously found that BPs displayed a general pattern of increased functional connectivity of the dorsolateral prefrontal cortex (DLPFC), insula, thalamus, inferior parietal cortex and cerebellum with many brain area compared to UPs and controls (Benson et al., 2008). In this study, we focused on the amygdala and hippocampus and postulated they would also exhibit a pattern of metabolic hyperconnectivity in BPs and hypo-connectivity in UPs similar to that seen in cortical and thalamic regions (Benson et al., 2008; Willis et al., 2008). In addition, because of reports in UPs of increased left amygdalar and reduced right hippocampal volumes (Mervaala et al., 2000), we hypothesized that in UPs the connectivity would differ as a function of laterality.

2. Methods and materials

2.1. Subjects

The subjects involved in this study, as detailed previously in Benson et al. (2008), Willis et al. (2008), are described in Table 1. Thirty treatment-refractory inpatients with bipolar disorder (18 men (M) and 12 women (F); mean age: 36.4 ± 10.6 [mean $\pm$ SD], days med-free: 29.8 ± 38.3; Ketter et al., 2001) and 34 patients with unipolar depression, including treatment-refractory inpatients (Kimbrell et al., 2002) as well as outpatients with less challenging illness (Little et al., 1996, 2005) (18 M and 21 F; mean age: 43.0 ± 13.3; days med-free 68.9 ± 95.1) were imaged medication-free. The mean age of the two patients groups slightly differed ($t=2.20$, $p=0.03$, $df=62$), which was controlled statistically (see below). All patients were assessed with ratings of depression, mania, and anxiety on the day of the scan (Hamilton, 1960; Beck, et al., 1961; Young et al., 1978; Spielberger et al., 1983).

Clinical characteristics, including illness severity, time-course measures, comorbidity, and family history were collected, in some instances on a subset of the patients (BP, $n=26$; UP, $n=30$). The two patient groups had comparable levels of illness severity as assessed by number of ratings of depression, anxiety, failed medication trials, and refractory indices. One discrepancy, was the increased number of prior depressive episodes in BPs ($t=-3.64$, $p=0.001$, $df=54$). However, weeks-ill was not significantly different, suggesting shorter episodes accompanied the greater cyclicity in BPs. Comorbid diagnoses included anxiety disorders (BP: $n=4$, UP: $n=5$) and substance abuse (BP: $n=4$, UP: $n=7$). Family history broke down as follows: (1) in BPs, bipolar illness ($n=11$), depression ($n=6$), anxiety ($n=4$), and substance abuse ($n=3$); and (2) in UPs, bipolar illness ($n=2$), depression ($n=13$), one with anxiety ($n=1$), and substance abuse ($n=2$).