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Review

Diagnostic and clinical implications of functional neuroimaging in bipolar disorder

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ABSTRACT

Advances in functional neuroimaging have ushered in studies that have enhanced our understanding of the neuropathophysiology of bipolar disorder, but do not yet have clinical applications. We describe the major circuits (ventrolateral, dorsolateral, ventromedial, and anterior cingulate) thought to be involved in the corticolimbic dysregulation that may underlie mood states in patients with bipolar disorder. The potential clinical application of functional neuroimaging in bipolar disorder is considered in terms of prognostic, predictive, and treatment biomarkers. To date, most research has focused on prognostic biomarkers to differentiate patients with bipolar disorder from those with other affective or psychotic diagnoses, or healthy subjects. The search for treatment biomarkers, which suggest mechanisms of pharmacodynamic or treatment response, and predictive biomarkers has thus far involved only pediatric patients diagnosed with bipolar disorder. The results to date are encouraging and suggest that functional neuroimaging may be of eventual benefit in determining biomarkers of treatment response. Further refinement of biomarker identification, and perhaps even illness characterization are needed to find prognostic and predictive biomarkers of bipolar disorder.

1. Introduction

Bipolar disorder, characterized by recurrent mood episodes, affects at least 3% of the population (Kessler et al., 2005). In bipolar I disorder, patients experience episodes of abnormally elevated mood (mania) and most often (although not required diagnostically) depression. Bipolar II disorder is similar, though patients experience milder episodes of elevated mood (hypomania) and depressive episodes are required. Over the course of the illness, patients with bipolar disorder spend much more time with depressive compared to mood elevation symptoms (Judd et al., 2003).

The underlying neurobiology of bipolar disorders has been investigated through the use of brain imaging, with functional neuroimaging playing a major role in helping to detect altered brain networks and regions. Links between clinical symptomology and underlying neural changes raise the important issue of whether neuroimaging can contribute to the definition of biomarkers related to bipolar disorder. In this review, we focus primarily on functional neuroimaging findings that are relevant to the search for potential biomarkers of bipolar disorders. (Other reviews have provided more detailed general surveys of cerebral metabolic studies (Brooks et al., 2010b) and fMRI findings (Altshuler and Townsend, 2012; Chen et al., 2011; Phillips and Swartz, 2014).)

Savitz et al. (Savitz et al., 2013) discussed important considerations for using brain imaging to detect biomarkers in mood disorders. In particular, they noted the distinction between (a) *prognostic* biomarkers, which are baseline characteristics that identify risk for disease or disease progression, (b) *predictive* biomarkers, which predict the likelihood of response to a treatment, and (c) *treatment* (or pharmacodynamic) biomarkers, which provide evidence of treatment effects. There is not necessarily overlap among the types of biomarkers, because a prognostic biomarker may not meet requirements of a treatment biomarker. Indeed, treatment biomarkers may vary according to type of treatment. Because verification of biomarkers requires longitudinal measures, reliability of functional brain imaging and patient-specific factors can affect the likelihood of biomarker detection.

In this review, limit discussion to functional neuroimaging studies that have used either positron emission tomography in conjunction with ^{18}flourodeoxyglucose (^{18}FDG-PET) or functional magnetic resonance imaging (fMRI). ^{18}FDG-PET is an imaging modality that involves measurement of regional uptake of radioactive glucose in the brain. A limitation of PET is that delay in isotope

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uptake precludes 'real-time' observation of brain function. Moreover, the typical spatial resolution of PET scans is not high as in other imaging modalities. fMRI is a noninvasive procedure that provides an indirect measure of neural activity during task performance yielding fairly high-resolution images of blood oxygen level dependent (BOLD) activity. While advantageous for spatial resolution, the BOLD signal of fMRI develops slowly, which results in poor temporal resolution. Often this tradeoff is reasonable to obtain real-time functional data. More detailed descriptions regarding imaging modalities and their application to the study of bipolar disorder may be found elsewhere (Adler et al., 2012).

We will first describe a prevailing model of the neural underpinnings of bipolar disorder to provide a context for functional neuroimaging findings. Next, we consider existing literature in terms of the three types of biomarkers. In our discussion of research that could lead to prognostic biomarkers, we review changes in brain function associated with acute mood states of depression, mania, and normal (euthymic) mood as well as initial work in the area of differential diagnosis of bipolar disorder. Research related to predictive and treatment biomarkers in bipolar disorder is limited, but we describe initial work that has been performed.

2. Neural model of bipolar disorder

Neural models of bipolar disorder have entailed variants of what has been referred to as a corticolimbic (Anand et al., 2009; Brooks, Hoblyn, Woodard, Rosen, & Ketter, 2009a) or anterior limbic (Adler et al., 2006; Strakowski et al., 2005) model, which is illustrated in Fig. 1. The corticlolimbic model was used to explain altered emotional control after consensus meetings of researchers in bipolar disorder (Strakowski et al., 2012) and further elaborated in a review of functional neuroimaging findings in emotion regulation (Phillips and Swartz, 2014). The circuits described in the consensus model were proposed to account for internal and external emotional control along with cognition. Thus, a ventrolateral circuit appears to process external emotional stimuli automatically (Phillips and Swartz, 2014) and a ventromedial circuit to process internally-generated emotion (Phillips et al., 2008a). An additional anterior cingulate circuit was proposed to integrate emotional and cognitive output to modulate behavior. Although many of the structural components of the circuits are interconnected through the amygdala (a subcortical brain structure primarily involved with regulation of fear of potentially threatening stimuli (Fusar-Poli et al., 2009)), for ease of relating them to clinical phenomena, we discuss each of these circuits separately in the context of proposed control functions.

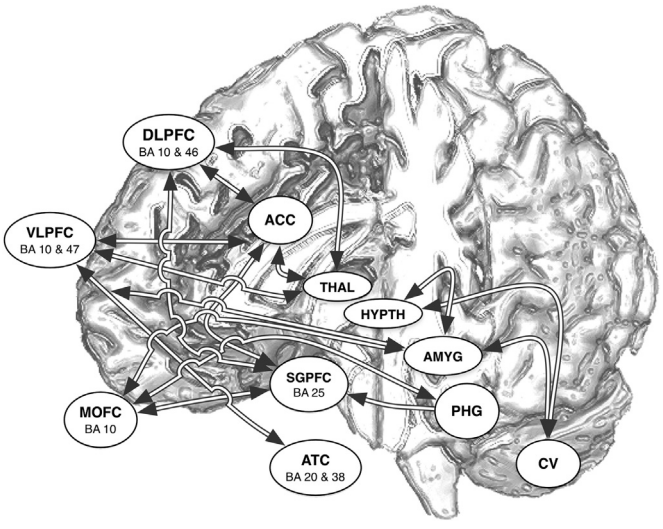

Fig. 1. Key regions of the corticolimbic network and their major network connections relevant to bipolar disorder (Brooks et al., 2009a) ACC = Anterior cingulate, AMG = Amygdala, ATC = Anterior Temporal Cortex, CV = Cerebellar vermis, DLPFC = Dorsolateral prefrontal cortex, HYPTH = Hypothalamus, MOFC = Medio-orbital prefrontal cortex, PHG = Parahippocampal gyrus, SGPFC = subgenual prefrontal cortex, THAL = Thalamus, VLPFC = Ventrolateral prefrontal cortex.

2.1. Ventrolateral circuit

The ventrolateral circuit, illustrated in Fig. 2, includes the ventrolateral prefrontal cortex, generally defined as Brodmann's areas (BA) 10 & 47. Output from the ventrolateral prefrontal cortex is routed to the ventromedial striatum (which includes the ventromedial caudate, ventral putamen, nucleus accumbens, and olfactory tubercle), then to the globus pallidus, and finally to the thalamus, which regulates emotional expression. The circuit is completed by fibers from the thalamus that project back to the ventrolateral prefrontal cortex (Almeida et al., 2009). The anterior temporal cortex, including BA 20 and 38, provides input to the ventrolateral circuit through its reciprocal connections with the ventrolateral prefrontal cortex and the amygdala. Within the ventrolateral circuit, abnormalities of the globus pallidus and ventromedial striatum are thought to precede illness onset, whereas those in the ventrolateral prefrontal cortex may arise afterwards (Strakowski et al., 2012).

2.2. Ventromedial circuit

The ventromedial circuit, depicted in Fig. 3, includes part of the ventromedial prefrontal cortex defined by BA 11, whose output is directed to the nucleus accumbens and onward to the thalamus. The thalamus completes a feedback loop through its projections back to the ventromedial prefrontal cortex. The ventromedial prefrontal cortex, nucleus accumbens, and thalamus all maintain reciprocal connections to the amygdala. The insula is involved in the ventromedial circuit through its reciprocal communications with the amygdala and the ventromedial prefrontal cortex (Strakowski et al., 2012). Both the globus pallidus and the nucleus accumbens are thought to exhibit abnormalities antecedent to the onset of bipolar disorder (Strakowski et al., 2012).

2.3. Dorsolateral circuit

As shown in Fig. 4, the dorsolateral circuit includes BA 9 and 10 in the dorsolateral prefrontal cortex, which project to the globus pallidus through the caudate nucleus. This region projects to the ventral anterior and mediodorsal thalamus, which project in turn back to BA 9 and 10 to complete the circuit (Almeida et al., 2009).

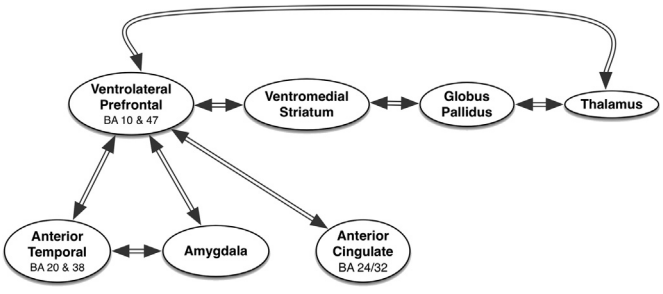

Fig. 2. Regions involved in the ventrolateral prefrontal circuit.