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ScienceDirect
Psychiatry Research: Neuroimaging 164 (2008) 30–47
PSYCHIATRY RESEARCH NEUROIMAGING
www.elsevier.com/locate/psychresns

Interregional cerebral metabolic associativity during a continuous performance task (Part II) : Differential alterations in bipolar and unipolar disorders

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Received 27 July 2006; received in revised form 17 October 2007; accepted 22 December 2007

Abstract

Unipolar and bipolar disorders have often been reported to exhibit abnormal regional brain activity in prefrontal cortex and paralimbic structures compared with healthy controls. We sought to ascertain how regions postulated to be abnormal in bipolar and unipolar disorders were functionally connected to the rest of the brain, and how this associativity differed from healthy controls. Thirty patients with bipolar disorder (BPs), 34 patients with unipolar disorder (UPs), and 66 healthy volunteers (Willis, M.W., Benson, B.E., Ketter, T.A., Kimbrell, T.A., George, M.S., Speer, A.M., Herscovitch, P., Post, R.M., 2008. Interregional cerebral metabolic associativity during a continuous performance task in healthy adults. Psychiatry Research: Neuroimaging 164 (1)) were imaged using F-18-fluorodeoxyglucose and positron emission tomography (FDG-PET) while performing an auditory continuous performance task (CPT). Five bilateral regions of interest (ROIs), namely dorsolateral prefrontal cortex (DLPFC), insula, inferior parietal cortex (INFP), thalamus and cerebellum, were correlated with normalized cerebral metabolism in the rest of the brain while covarying out Hamilton Depression Rating Scale Scores. In bipolar patients compared with controls, metabolism in the left DLPFC and INFP, and bilateral thalamus and insula had more positive and fewer negative metabolic correlations with other brain regions. In contrast, compared with controls, unipolar patients had fewer significant correlative relationships, either positive or negative. In common, bipolar and unipolar patients lacked the normal inverse relationships between the DLPFC and cerebellum, as well as relationships between the primary ROIs and other limbic regions (medial prefrontal cortex, anterior cingulate, and temporal lobes) compared with controls. Associations of DLPFC and INFP with other brain areas were different in each hemisphere in patients and controls. Bipolar patients exhibited exaggerated positive coherence of activity throughout the brain, while unipolar patients showed a paucity of normal interrelationships compared with controls. These abnormal patterns of metabolic associativity suggest marked interregional neuronal dysregulation in

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0925-4927/$ - see front matter. Published by Elsevier Ireland Ltd.
doi:10.1016/j.pscychresns.2007.12.016

bipolar and unipolar illness exists beyond that of mere absolute regional differences from control levels, and provides rationale for using acute and long-term therapies that may re-establish and maintain normal associativity in these devastating illnesses.
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Keywords: Associativity; Functional connectivity; Affective disorders; Metabolism; FDG; Neuroimaging; Depression; Mania; Bipolar; Unipolar

1. Introduction

Functional brain imaging studies using either ^{15}O water or ^{18}F-fluorodeoxyglucose (FDG) measuring blood flow or metabolism, respectively, have usually revealed decreased activity in prefrontal lobe areas in both unipolar and bipolar affective disorders in comparison to healthy controls (see reviews, Dougherty and Rauch, 1997; Ketter et al., 1997; Drevets, 1998; Strakowski et al., 2005). Within different subregions of the frontal lobe, such as dorsolateral, medial, or orbital, more diverse findings of increases and decreases have been reported in subgroups of depressed patients (Drevets et al., 1995). In general, however, the degree of dorsolateral prefrontal cortex hypoactivity correlates inversely with severity of depression measured on the Hamilton Depression rating scale (HDRS; Hamilton, 1960) in both the primary and secondary affective disorders (Baxter et al., 1989; Drevets et al., 1992; Benson et al., 1997; Kimbrell et al., 2002). Moreover, the severity of depression often correlated positively with amygdala activity (Drevets et al., 1992; Abercrombie et al., 1998) and negatively with the anterior cingulate (Benson et al., 1997; Kimbrell et al., 2002).

In other brain areas, however, there has been more heterogeneity in findings. This has generally been attributed to differences in clinical populations with respect to: degrees of illness severity and comorbidity (Ketter et al., 2001; Kimbrell et al., 2002); treatment refractoriness (Ketter et al., 2001; Kimbrell et al., 2002); genetic or familial subtype (Drevets et al., 1995); type of neuropsychological task utilized; and illness characteristics, such as psychomotor retardation or cognitive deficits (Dunn et al., 2002).

Another possibility that could account for the discrepancies in the reported levels of activity in affective illnesses is altered patterns of associativity among these regions, which might signify neural dysregulation. For the purpose of this study, associativity will be defined as the correlative metabolic relationships between brain regions, often termed as functional connectivity (Horwitz, 2003). Abnormal cerebral functional relationships among different regions may account for some of the emotional, cognitive, and behavioral dysfunctions of depression, even when absolute or relative regional differences from controls are small or absent. If, in fact, these diseases arise from abnormal associativity, remission may occur when normal associativity resumed, either due to time, talking therapy, medications, or ECT. Such associative dysfunction would contrast with Alzheimer's dementia, for example, where documented neural loss in temporal–parietal areas is associated with clear-cut hypometabolism compared with age-matched controls (Grady et al., 1988). While small degrees of glial and neuronal cell loss in the subgenual anterior cingulate have been reported in affectively ill patients (Drevets et al., 1997; Rajkowska et al., 1999), altered regional activity is not always observed. Conversely, in the absence of structural abnormalities (measured by MRI) in the subgenual area, activity in this region correlated with increased delta activity and exhibited decreased metabolism in melancholics, but not nonmelancholic depression or controls (Pizzagalli et al., 2004).

As the psychiatric illnesses have increasingly been recognized as not only potentially related to aberrant areas of activation, but also abnormal patterns of associative learning (Kandel, 1999), one might expect patterns of neural associativity to show abnormalities even in the absence of discrete areas of pathological increases or decreases in activity from normal. Functional connectivity models aim to emulate the complex neuronal circuits that are theorized to be important in the modulation of emotion, cognition, and behavioral activation. For example, it may be possible to determine whether the cortico-striatal-thalamic loops (Alexander et al., 1990) are dysregulated in affective and schizophrenic syndromes as theorized (Ongur and Price, 2000; Cummings, 1997; Carlsson et al., 2000).

Abnormal functional connectivity has been reported in major depression (Mallet et al., 1998; Anand et al., 2005), schizophrenia (Clark et al., 1984; Katz et al., 1996; Friston et al., 1996; Buchsbaum et al., 1999; Mallet et al., 1998; Andreason et al., 1999; Meyer-Lindenberg et al., 2001), obsessive–compulsive disorder (Horwitz et al., 1991; Mallet et al., 1998), and Down's syndrome (Horwitz et al., 1990). Mayberg and colleagues (Seminowicz et al., 2004; Mayberg, 2002) have applied structural equation modeling to develop effective connectivity models in unipolar illness, which differentiate antidepressant and psychotherapy responders from nonresponders. To date,