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Interregional cerebral metabolic associativity during a continuous performance task (Part I): Healthy adults

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Abstract

One emerging hypothesis regarding psychiatric illnesses is that they arise from the dysregulation of normal circuits or neuroanatomical patterns. In order to study mood disorders within this framework, we explored normal metabolic associativity patterns in healthy volunteers as a prelude to examining the same relationships in affectively ill patients (Part II). We applied correlational analyses to regional brain activity as measured with FDG-PET during an auditory continuous performance task (CPT) in 66 healthy volunteers. This simple attention task controlled for brain activity that otherwise might vary amongst affective and cognitive states. There were highly significant positive correlations between homologous regions in the two hemispheres in thalamic, extrapyramidal, orbital frontal, medial temporal and cerebellar areas. Dorsal frontal, lateral temporal, cingulate, and especially insula, and inferior parietal areas showed less significant homologous associativity, suggesting more specific lateralized function. The medulla and bilateral thalami exhibited the most diverse interregional associations. A general pattern emerged of cortical regions covarying inversely with subcortical structures, particularly the frontal cortex with cerebellum, amygdala and thalamus. These analytical data may help to confirm known functional and neuroanatomical relationships, elucidate others as yet unreported, and serve as a basis for comparison to patients with psychiatric illness.
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Keywords: Positron emission tomography (PET); Cerebral glucose metabolism; FDG; Normal; Connectivity; Neural circuitry

1. Introduction

Functional imaging studies attempting to delineate the neural substrates of the mood disorders have been plentiful in recent years, but the findings have often proved disparate and conflicting. For instance, in

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depressed patients compared with matched controls, anterior cingulate activity has been reported as increased among responders (Drevets et al., 1992; Mayberg et al., 1997) and decreased among nonresponders (Bench et al., 1992; Mayberg et al., 1997), thalamic function increased (Brody et al., 2001) and decreased (Austin et al., 1992) and parietal function increased (Abou-Saleh et al., 1999) and decreased (Mayberg et al., 1997). Even the most consistent finding in depression, decreased baseline dorsolateral prefrontal activity, has been contradicted by at least one recent study (Brody et al., 2001).

Similarly, few functional deficits specific to bipolar illness have been consistently identified (Strakowski et al., 2000). Much of the observed heterogeneity can be attributed to: methodological variation; the existence of multiple illness subtypes, severities, and co-morbidities; and state versus trait distinctions. However, one hypothesis that could help explain divergent findings is that mean group differences between patients and controls do not fully characterize metabolic abnormalities in the illnesses in question, especially given the possibility of pathway-related alterations and compensatory mechanisms arising in illness (Sackeim, 2001). One region in particular, the thalamus, has been suggested to play a role in neural circuits gone awry in both bipolar disorder and schizophrenia (Buchsbaum et al., 1997). This is a key way station not only in somatomotor integration but also in the series of modulatory cortical–striatal–thalamic loops described by Alexander et al. (1990). Investigations are now beginning to focus on possible abnormalities in the interaction, or functional connectivity, among the various regions believed to play a part in the recognition, expression and regulation of affect in a variety of illnesses (Mallet et al., 1998). A necessary foundation for this area of study is the identification of functional circuits involved in normal mood regulation as well as emotional and cognitive processing of the environment.

Several methods have been introduced for this type of inquiry, among them eigenimage analysis (Friston et al., 1993), scaled subprofile modeling (Moeller et al., 1987), and direct covariance of regions (Horwitz, 1991a). Zald et al. (1998) have investigated the complementary information that can be derived from the latter paradigm using both nonsubtracted (single task) and subtracted (between task) correlational data in order to control for static influences (e.g., blood supply, gray/white ratios, etc.) that may dominate interregional covariances, and which should be a concern with any examination of this kind. In this regard, several studies have examined interregional covariance 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; Andreasen et al., 1999; Meyer-Lindenberg et al., 2001), obsessive-compulsive disorder (Horwitz et al., 1991b; Mallet et al., 1998), and Down's syndrome (Horwitz et al., 1990).

Because we wished to generate normal baseline associativity maps to use in the subsequent investigation of couplings between arbitrary pairs of regions in affectively ill patients, and to keep the data accessible to the widest audience, we favored a simple correlational approach. In this report, we employ a single-task covariance approach in a study of 66 healthy volunteers to characterize in a descriptive fashion normal metabolic regional covariance during an emotionally neutral and cognitively non-challenging auditory continuous performance task (CPT). We choose to measure metabolic activity during a simple attention task (a task is a prerequisite of connectivity studies) in attempt to entrain mental activity, with the goal of reducing the variable cognitive states that may be associated with REST condition. Furthermore, the REST condition is not considered a zero-activity period (Stark and Squire, 2001), but constitutes an uncontrolled condition that is difficult to assess and may be ambiguous as a baseline condition.

The interregional covariance method applied to a single condition scanning reveals correlative relationships that may arise from a variety of factors, including congruency in cytoarchitecture and gray/white ratios as well as actual neuronal communication (i.e., functional connectivity) between the regions examined. However, within the limits of this method and its interpretation, this exploratory analysis serves as a descriptive narrative to further define interregional associations of cerebral metabolism during a CPT task in normal volunteers. In conjunction with the companion paper, it also provides a normal baseline to which our unipolar and bipolar affectively ill patients can be compared (Benson et al., 2008, Part II).

2. Methods

2.1. Subjects

Healthy adult volunteers were recruited from the surrounding community through the Clinical Research Volunteer Program at the National Institutes of Health (NIH). Applicants were excluded if they had any personal or first-degree relative history of psychiatric illness or substance abuse as determined by a structured interview using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000). Other exclusionary criteria included

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