Psychiatry Research: Neuroimaging 193 (2011) 144–150

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Failure to segregate emotional processing from cognitive and sensorimotor processing in major depression

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ARTICLE INFO

Article history:
Received 6 September 2010
Received in revised form 29 December 2010
Accepted 18 January 2011

Keywords:
fMRI
Ventral striatum
Functional connectivity
Principal component analysis
Default mode network
Neuroimaging

ABSTRACT

Most functional neuroimaging studies of major depressive disorder (MDD) employ univariate methods of statistical analysis to localize abnormalities of neural activity. Less has been done to investigate functional relations between these regions, or with regions not usually implicated in depression. Examination of intraneuronal and interneural network relations is important for the advancement of emerging network models for MDD. Principal component analysis (PCA), a multivariate statistical method, was used to examine differences in functional connectivity between 10 unmedicated patients with MDD and 12 healthy subjects engaged in a positive word viewing task. In healthy subjects, principal component (PC) 1 (33% variance) revealed functional connectivity of task-specific sensory, linguistic, and motor regions, along with functional anticorrelations in the default mode network; PC2 (10% variance) displayed functional connectivity of areas involved in emotional processing. This segregation of functions did not occur in the depressed group, where regions involved in emotional functions appeared in PC1 (34% variance) co-varying with those involved in linguistic, motor, and default mode network processing. The lack of segregation of emotional processing from cognitive and sensorimotor functions may represent a systems level neural substrate for a core phenomenon of depression: the interconnection of affective disturbance with experience, cognition, and behavior.

1. Introduction

Functional neuroimaging studies of major depressive disorder (MDD) have provided important insights into this highly prevalent and disabling illness, elucidating the neural underpinnings of constituent symptoms such as anhedonia and negative self-perception, differences and commonalities among depressive subtypes, and mechanisms of treatment (Dougherty and Rauch, 2007; Drevets et al., 2008; Price and Drevets, 2010). Most studies of depression have employed univariate methods of statistical analysis to identify localized abnormalities of neural activity, with findings converging on a number of regions including the subgenual cingulate (B25), anterior cingulate (B24/32), lateral prefrontal (B9/46), dorsomedial prefrontal (B32), medial frontal (B10), orbital frontal (B11) and insular cortices, hippocampus, amygdala, striatum and thalamus (Drevets et al., 1992, 1997; Mayberg et al., 1999; Mayberg, 2003; Seminowicz et al., 2004; Grimm et al., 2009a, 2009b). Less has been done, on a neural systems level, to investigate functional relations between these regions or with regions and functions not usually implicated in depression. Examination of such intraneural and interneural network relations is important for the continued development of emerging network models of MDD.

Of the few studies that address these questions, most have examined connectivity between predetermined regions of interest (ROI) including fronto-cingulate regions (Schlosser et al., 2008), right and left amygdalae (Irwin et al., 2004), anterior cingulate and amygdala, pallidostriatum and medial thalamus (Anand et al., 2005), and amygdala, hippocampus and striatum (Hamilton and Gotlib, 2008). Others have examined connectivity within the context of a seven-region model of depression (Seminowicz et al., 2004) or used seed-based methods that detect temporal correlation between a predefined region (seed) and all other brain regions (Zhang and Raichle, 2010), planting seeds in orbitofrontal cortex (Frodl et al., 2010), precuneus/posterior cingulate cortex (posterior default mode network) (Bluhm et al., 2009; Sheline et al., 2010), dorsolateral

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doi:10.1016/j.pscychresns.2011.01.012

prefrontal cortex (Sheline et al., 2010), subgenual anterior cingulate (Sheline et al., 2010) and caudate nuclei (Kenny et al., 2010).

A different approach to investigating functional connectivity is provided by component-based multivariate analyses that use advanced computational statistical methods to decompose functional data into statistically distinct connectivity maps, or components. Components represent temporal correlations between spatially remote neurophysiologic events believed to represent functionally bound neural networks (Friston, 1994). Multivariate methods of this type identify both both intraneural and interneural network relations, elucidating patterns of brain function that may not be revealed by methods relying on predefined regions of interest, and have proved useful in providing insight into a variety of phenomena including sex differences in neurocognition (Butler et al., 2007) and default mode network abnormalities in schizophrenia (Garrity et al., 2007).

To date, few functional neuroimaging studies have employed component-based, multivariate approaches to investigate functional connectivity in depression. Greicius et al. used independent component analysis (ICA), a method that separates a multivariate signal into maximally independent sources, to compare default mode networks of depressed and healthy subjects at rest, and found increased functional connectivity of subgenual cingulate and thalamus with the default mode network of depressed subjects (Greicius et al., 2007). Vasic et al. also used ICA in the context of a working memory task to reveal aberrant functional connectivity in dorsolateral prefrontal and cingulate networks in depressed subjects (Vasic et al., 2009). To our knowledge, no studies to date have used component-based multivariate approaches to examine functional connectivity in depressed subjects engaged in affective processing – a mental function of central relevance to MDD that has reliably shown differences between depressed subjects and healthy controls (Epstein et al., 2006; Strigo et al., 2008; Peluso et al., 2009).

Principal component analysis (PCA) is another statistical technique that transforms multiple possibly correlated variables into a smaller number of orthogonal variables, termed principal components, with each successive component accounting for as much of the data variance as possible. Thus, the internal structure of a complex functional magnetic resonance imaging (fMRI) data set can be represented by a few major components, each consisting, in turn, of the *intercorrelated* activity of neural regions presumed to operate as a functional network in mediating a given component of a task or resting state (Friston et al., 1993; Friston, 1994). Here, we employ principal component analysis to examine functional connectivity in unmedicated depressed and healthy subjects engaged in affective processing, providing complementary information to that obtained by a univariate analysis performed previously on data from the same group of patients (Epstein et al., 2006). In the previous analysis, we identified regional abnormalities in depressed (versus healthy) subjects viewing positively valenced words, confirming our hypothesis of decreased ventral striatal response to positive stimuli in depressed subjects. In the current report, we apply PCA to that data set to examine intraneural and interneural network relations.

2. Methods

For further details on methods described below, refer to Epstein et al. (2006).

2.1. Participants

Subjects were 10 unmedicated patients (mean age = 35.6, 9 females, 1 male; 8 right-handed, 2 left-handed; 2 medication naive, 8 with 3 months' minimum duration off medication, range: 3 months to 11 years off medication) with DSM-IV major depression (mean Hamilton Depression Rating Scale score 28.5, S.D. = 5.2) as assessed with the Structured Clinical Interview for DSM-IV (SCID) and 12 healthy controls (mean age = 32.0; 7 females, 5 males; all right-handed). All participants were free of other major psychiatric diagnoses and significant neurological or medical disorders. Informed consent and study approval were obtained in accord with the New York-Presbyterian Hospital Institutional Review Board.

2.2. Paradigm

Stimuli consisted of 24 positive, 24 negative and 24 neutral words presented visually in 12 six-word blocks interspersed with a visual fixation "rest" condition. Subjects were instructed to read each word silently, then press a button located beneath their right index fingers.

2.3. Image acquisition

All functional image data were acquired with a GE Signa 3 Tesla MRI scanner using blood oxygen level dependent (BOLD) contrast imaging. After shimming to maximize homogeneity, a series of functional scans was acquired with gradient echo-planar imaging (EPI) (TR = 1200; TE = 30; flip angle = 70; field of view = 240 mm; 15 slices; 5 mm thickness with 1 mm interslice space; matrix = 64 × 64), and a modified *z*-shimming algorithm to reduce susceptibility artifact at the base of the brain (Gu et al., 2002). Echo-planar images were acquired in the axial plane parallel with the anterior commissure–posterior commissure (AC–PC) plane. A reference T1-weighted anatomical image was acquired immediately prior to EPI acquisition. A high-resolution T1-weighted anatomical image using a spoiled-gradient (SPGR) sequence with a resolution of $0.9375 \times 0.9375 \times 1.5\ mm^3$ was also acquired.

2.4. Image processing and analysis

Image processing was performed within a customized Statistical Parametric Mapping software package (www.fil.ion.ucl.ac.uk/spm), which included manual AC–PC reorientation of all anatomical and echo-planar images; realignment of functional echo-planar images based on intracranial voxels (3 × 3 × 3 mm) to correct for slight head movement between scans; coregistration of functional echo-planar images to the corresponding anatomical image based on the transformation of the reference anatomical image to the latter for each individual subject; stereotactic normalization to the standardized coordinate space of Talairach and Tournoux (Montreal Neurological Institute [MNI] average of 152T1 brain scans) based on the high-resolution anatomical image; and spatial smoothing of the normalized echo-planar images with an isotropic Gaussian kernel (7.5 mm, full width at half maximum). Note that the mask image of intracranial voxels shared commonly by all subjects was used as the spatial mask.

For image data analyses, first, a whole-brain voxel-by-voxel multiple linear regression model was employed at the individual subject level (Worsley et al., 2002). The resulting set of contrast–effect images and their corresponding standard deviation images was then used to create effect–size images (*z*-maps) to be entered into group level analyses.

The group level analyses examined the major spatial modes or eigenimages in three sets of PCA (Friston et al., 1993; Friston, 1994): one within the group of depressed subjects, one within the group of healthy controls, and one with the two groups combined. In the combined healthy-plus-depressed subject group, the eigenimages were examined based on their corresponding loading scores in association with group membership. Analyses were performed on the four blocks of positive words combined, as well as on the first two blocks (early) and the last two (late), to examine potential time effects (Protopopescu et al., 2005). For each configuration the normalized data matrix X_{NxM} (N participants under consideration by M voxels within the standardized brain space) of the effect of interest was subject to singular value decomposition in the form of $X_{N\times M} = U_{N\times N} \bullet S_{N\times N} \bullet V^T_{N\times M}$, where N columns of unitary orthogonal $V_{M\times N}$ are the resulting eigenimages (principal components) of the covariance matrix $X^T_{M\times N} X_{N\times M}$ (i.e., pair-wise/voxel-to-voxel