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

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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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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

functional connectivity matrix), $S_{N\times N}$ is a diagonal matrix of decreasing singular values (i.e., $S^2_{N\times N}=V^T_{N\times M}\bullet X^T_{M\times N}\bullet X_{N\times M}\bullet V_{M\times N}$ is a diagonal matrix of decreasing eigenvalues) and N columns of unitary orthogonal $U_{N\times N}$ are the corresponding loading score vectors. The first few eigenimages, covering 90% of the total variance, were examined. In the case of the two groups combined, the relation between group membership and the loading vector for each eigenimage interest was tested through correlation and thresholded at $p<0.05$ to reveal any statistically significant association between a spatial mode and group identity.

3. Results

Principal component (PC) 1 in healthy subjects (see Fig. 1) primarily demonstrated activations in visual cortex (calcarine cortex, middle and inferior occipital gyri), motor pathways (left precentral gyrus, bilateral putamen and cerebellar hemispheres), and anterior language regions (Broca's area); deactivations in PC 1 included regions of default mode network (precuneus, posterior cingulate and medial prefrontal cortex). In PC 2, healthy subjects primarily showed activations (ventral striatum, anterior cingulate, hippocampi, parahippocampi, superior

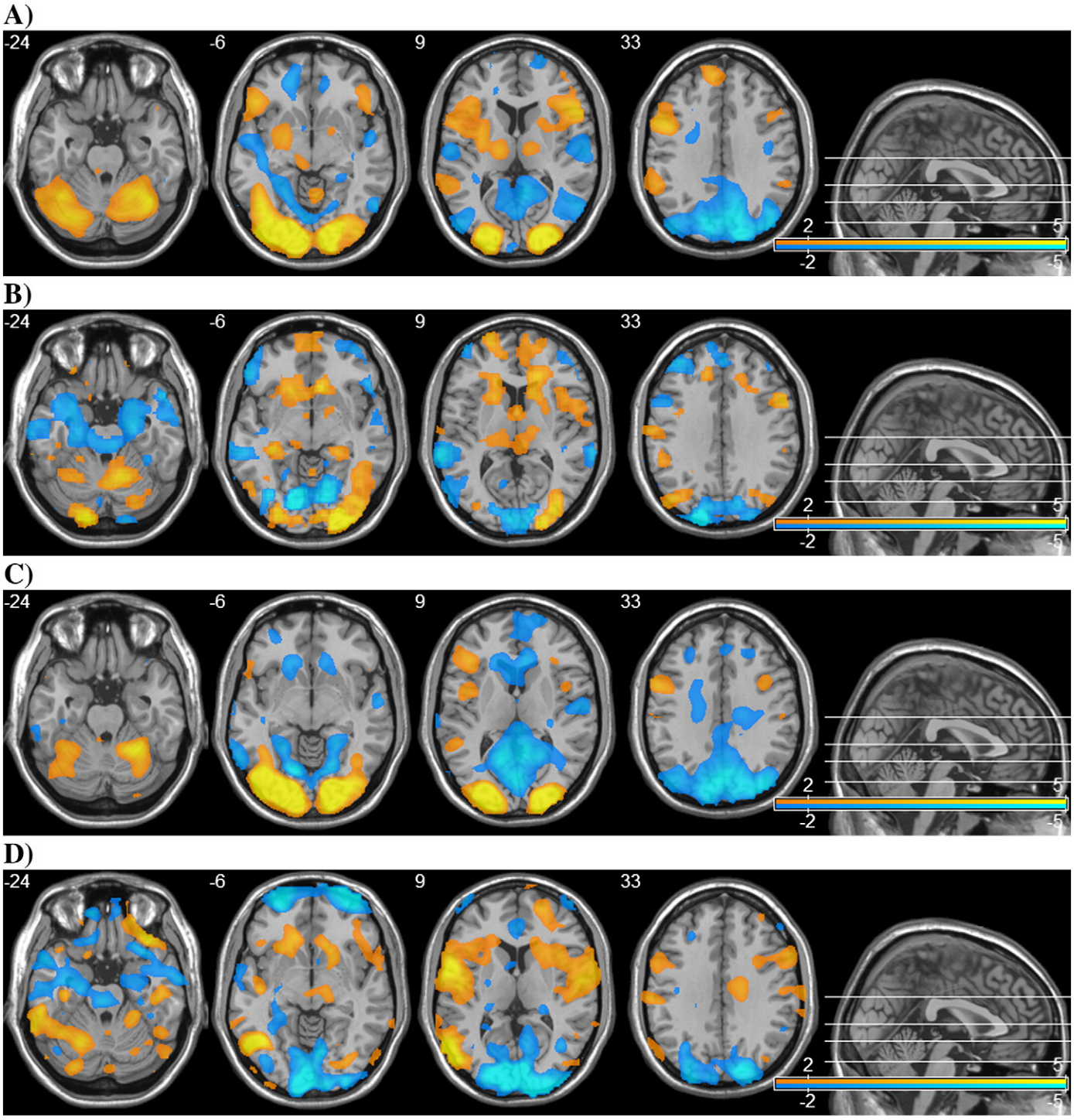

Fig. 1. Principal components 1 and 2 for healthy controls and depressed subjects. (A) Healthy controls: PC1 (32.79% variance). (B) Healthy controls: PC2 (10.35% variance). (C) Depressed subjects: PC1 (33.67% variance). (D) Depressed subjects: PC2 (13.79% variance). Note the presence of regions involved in affective processing in the first principal component in the depressed group (C).

frontal/superior medial frontal gyri) and deactivations (amygdalae, parahippocampi) in emotional processing regions. In depressed subjects, PC 1 revealed activations in visual cortex (calcarine cortex, superior/middle/inferior occipital gyri), motor pathways (bilateral precentral gyri, cerebellar hemispheres), anterior language regions (Broca's area) and emotional processing areas (bilateral insulae); deactivations also occurred in emotional processing regions (anterior cingulate, ventral striatum) and default mode network areas (precuneus, posterior cingulate, superior frontal/frontal gyri). See Tables 1 and 2 for complete listings of regions identified in PC 1 and 2 for healthy subjects and depressed patients; see Fig. 2 for a schematic representation of the findings.

In the combined group analysis of depressed-plus-healthy subjects (see Fig. 3A and B), group membership and loading score correlate significantly ($p = 0.047$) in the final two blocks of PC 3 (late effect). Given the limited sample size, this finding should be viewed as a trend with measured confidence. This component included activations in motor pathways (precentral gyri, cerebellar hemispheres, right putamen), anterior language regions (Broca's area) and deactivations in default mode network (precuneus, posterior cingulate, medial prefrontal cortex) and emotional processing areas (anterior cingulate, ventral striatum) as observed in PC1 of the depressed subjects. See Table 3 for a complete listing of regions identified in this combined group PC. There are no other significant correlations seen between group membership and principal components. As in the univariate analysis (Epstein et al., 2006), the neutral and negative word viewing conditions did not reveal robust, readily interpretable differences between depressed subjects and healthy controls.

4. Discussion

As might be expected in a paradigm involving reading of words and pressing of a button, in healthy subjects the first principal component demonstrated positive functional connectivity in sensory, linguistic, and motor processing regions (Fig. 1A). The co-activation included occipital cortex (visual processing) (Hubel et al., 1977), Broca's area (language processing) (Penfield and Roberts, 1959), left precentral gyrus (right index finger button press) (Kandel et al., 2000), and motor control/coordination areas in the cerebellar hemispheres and dorsal striatum (Thach et al., 1992; Wichmann and DeLong, 1996). The precuneus, posterior cingulate and medial prefrontal cortex – major nodes in the default mode network – were also part of this functional network, displaying anti-correlated activity consistent with the literature on default mode network deactivation during task performance (Raichle et al., 2001).

In the second principal component, healthy subjects demonstrated intercorrelation of areas involved in emotional processing, including regions implicated in positive word processing (ventral striatum) (Epstein et al., 2006), emotional self-regulation (anterior cingulate) (Bush et al., 2000), declarative and episodic memory (hippocampus) (Squire, 1992; Tulving and Markowitsch, 1998), and evaluation of self-related stimuli (right dorsal medial-prefrontal cortex [B10]) (Gusnard et al., 2001; Fossati et al., 2003; Northoff et al., 2006) (Fig. 1B). Bilateral amygdalar deactivations were also seen, consistent with previous findings of decreased amygdalar activity in positive conditions (LeDoux, 2000; Pollak et al., 2010).

Thus, healthy subjects displayed segregation of emotional processing (seen in PC 2) from sensory, linguistic, and motor functions (seen in PC 1). This segregation did not occur in the depressed group, where regions involved in emotional processing appeared in PC 1 and co-varied with those involved in sensory, linguistic, and motor network functions (PC 1). In particular, the ventral striatum, anterior cingulate, and insula co-varied with language and sensory motor regions (Fig. 1C). This lack of segregation is consistent with the literature on cognitive bias in depression (Deldin et al., 2001) and with the phenomenology of depression, in which an underlying affective disturbance colors the experience, cognition and behavior of the afflicted individual.

This difference in functional segregation was also seen in the combined depressed-plus-healthy group analysis, where it

Table 1
Principal component 1.

Healthy Controls	Depressed Patients
Activations	
B/L Calcarine Cortex(B17)	B/L Calcarine Cortex(B17)
B/L Middle/Inferior Occipital Gyri(B18)	B/L Superior/Middle/Inferior Occipital Gyri(B18)
L Precentral Gyrus(B6)	B/L Lingual Gyri(b18)
L Superior Medial Frontal Gyrus (B9/10)	B/L Pre and Post Central Gyri (L > R)(B6)
B/L Broca's Area (B45)	B/L Broca's Area (B45)
B/L Putamen	B/L Insulae(B47)
B/L Medial Thalami	B/L Cerebellar Hemispheres
B/L Cerebellar Hemispheres	B/L Midbrain
B/L Superior Colliculi	
Deactivations	
B/L Calcarine Cortex(B17)	B/L Cuneus(B18)
B/L Superior and Middle Occipital Gyri(B19/7)	B/L Precuneus(B7)
B/L Cuneus(B18)	B/L Lingual Gyri(B18)
B/L Precuneus(B7)	B/L Superior/Middle Temporal Gyri (R > L; B21/22)
B/L Posterior Cinguli(B23)	B/L Posterior Cinguli (B23/26)
B/L Lingual Gyri(B18)	B/L Superior/Middle Frontal Gyri(B9)
B/L Fusiform Gyri(B30)	B/L Anterior Cinguli(B32)
B/L Superior Temporal Gyri(B22/48)	B/L Ventral Striatum
B/L Middle Frontal Gyri(B9)	B/L Dorsal Striatum
B/L Superior Medial Frontal Gyri (B10/B11)	B/L Cerebellar Hemispheres
B/L Parahippocampi (with hippocampal extension)	R Superior Frontal Gyrus(B10)
B/L Cerebellar Hemispheres	R Frontal Gyrus(B10)
R Middle Temporal Gyrus(B20)	L Inferior Temporal Gyrus(B20)

Table 2
Principal component 2.

Healthy Controls	Depressed Patients
Activations	
B/L Precuneus(B30)	B/L Inferior Temporal Gyri(b20)
B/L Ventral Striatum (with dorsal extension)	B/L Insulae(B48)
B/L Anterior Cinguli (B24/32)	B/L Rolandic Operculum(B48)
B/L Superior Frontal Gyrus(B10)	B/L Mid Cinguli(B24/32)
B/L Superior Medial Frontal Gyrus(B10)	B/L Middle Orbital Frontal Gyri(B11)
B/L Hippocampi	B/L Middle Frontal Gyri(B46)
B/L Parahippocampi	B/L Dorsal Striatum (with ventral extension)
B/L Posterior Thalami	B/L Midbrain (R > L)
B/L Midbrain	B/L Superior Temporal Gyrus(B42/22)
B/L Cerebellar Hemispheres (anterior/medial)	R Postcentral Gyrus(B3/4)
Vermis	R Superior Frontal Gyrus(B10) L Fusiform Gyrus(B37)
Deactivations	
B/L Calcarine Cortex(B17)	B/L Calcarine Cortex(B19)
B/L Cuneus(B18/19)	B/L Superior and Middle Occipital Gyri(B18/19)
B/L Lingual GyriB18/19)	B/L Cuneus(B18/19)
B/L Superior/Middle/Inferior Temporal Gyri(B20-22/48)	B/L Anterior Cinguli (B32/24)
B/L Superior Temporal Poles(B38)	B/L Superior Orbital Frontal Gyrus(B11)
B/L Amygdalae	B/L Gyrus Recti(B11)
B/L Parahippocampi (with hippocampal extension)	B/L Hippocampi
B/L Superior Medial/Superior Frontal Gyri(B9)	B/L Pons
B/L Cerebellar Hemispheres	B/L Cerebellar Hemispheres Vermis

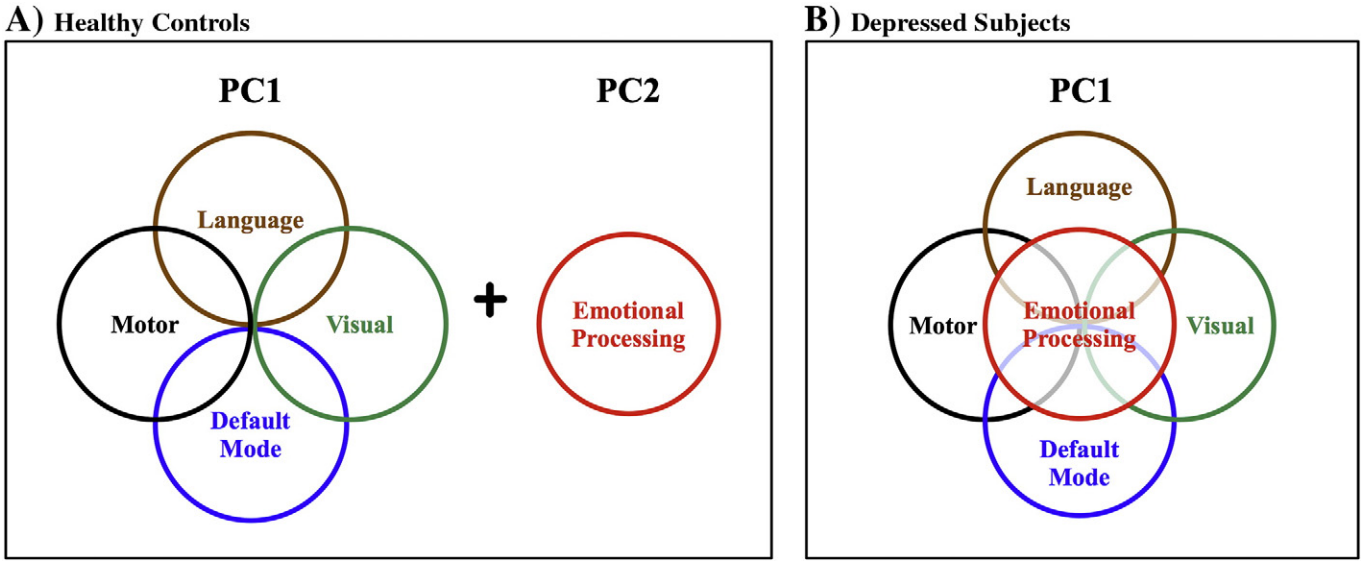

Fig. 2. Schematic depiction of interneural network connectivity patterns in healthy controls and depressed subjects.

differentiated between depressed and healthy subjects: the loading scores for the depressed patients are significantly lower than those for the healthy controls. Depression-related functionally interacting nodes include both limbic/paralimbic (anterior cingulate, ventral striatum, insula, and left hippocampus) and linguistic/motor/default mode regions (precentral gyrus, Broca's area, putamen, cerebellar

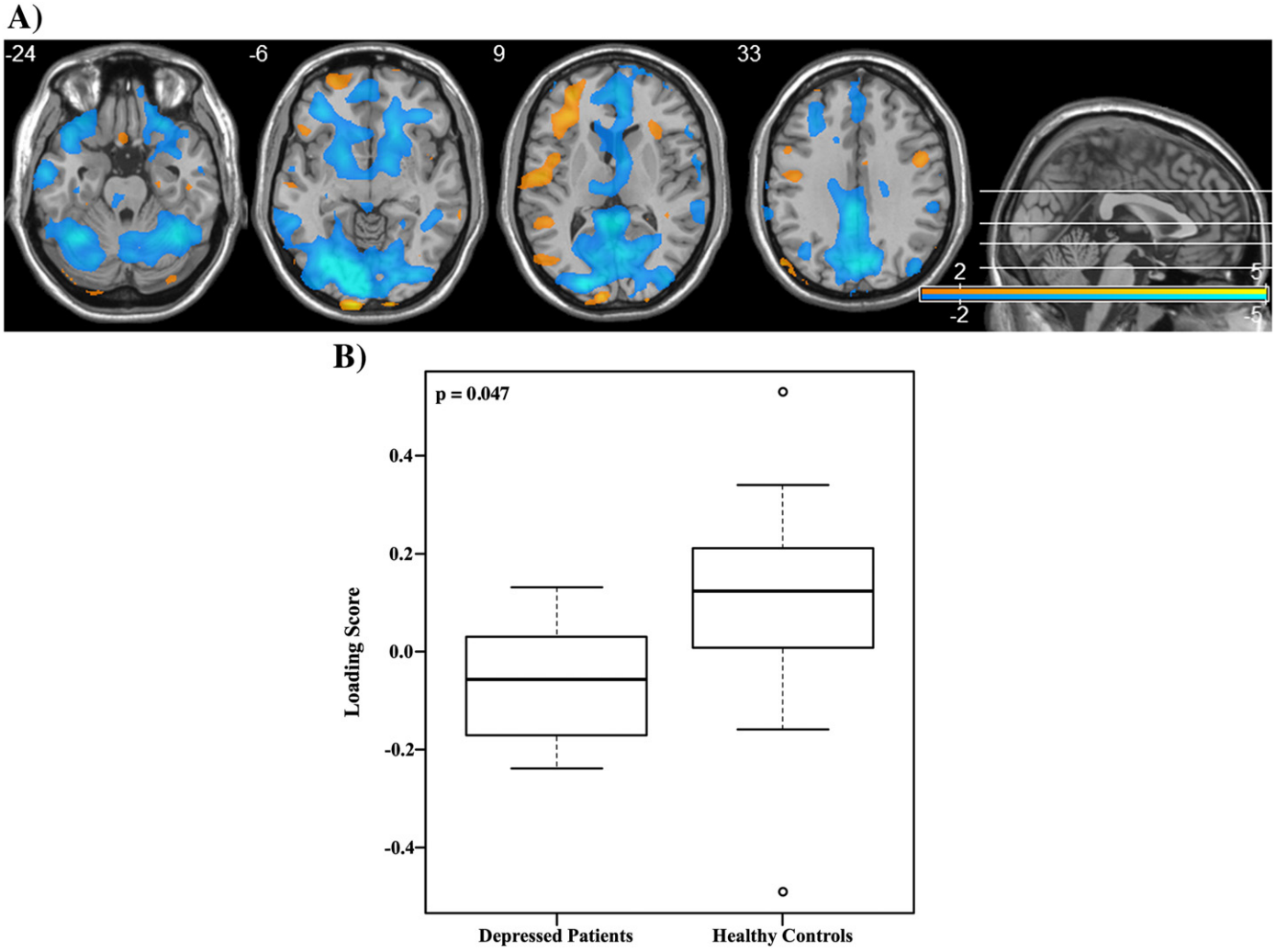

Fig. 3. (A) Combined depressed and healthy subjects group. This principal component was associated with depressed group membership ($p = 0.047$). (B) Loading score plot for combined depressed and healthy subject group. Note the trend towards lower loading scores for depressed compared to healthy control subjects.

Table 3
Combined PC3(late) depressed and healthy subject groups.

Activations
B/L Broca's Area (B45)
B/L Precentral Gyri(B6/9)
B/L Cerebellar Hemispheres
L Insula(B48)
L Middle Frontal Gyrus (B10/47)
L Superior Orbital Frontal Gyrus(b11)
L Superior/Middle/Inferior Temporal Gyri(B20/22)
R Middle Frontal Gyrus (B48)
R Putamen
R Midbrain (anterior)
R Pons (medial)
Deactivations
B/L Calcarine Cortex(B17)
B/L Middle and Inferior Occipital Gyri(B18)
B/L Cuneus(B18)
B/L Precuneus(B7)
B/L Lingual Gyri(B18)
B/L Fusiform Gyri(B37/19)
B/L Supramarginal Gyri(B48)
B/L Inferior Temporal Gyri(B20)
B/L Superior and Middle Temporal Poles(B38)
B/L Middle/Posterior Cinguli (B23)
B/L Anterior Cinguli (B24/32)
B/L Superior Medial/Superior Frontal Gyri (B9/10
B/L Medial/Inferior Orbital Frontal Gyri(B10/11/47)
B/L Rolandic Operculi(B48)
B/L Pre and Postcentral Gyri(B3/4/6)
B/L Ventral Striatum (with dorsal extension)
B/L Thalamus
B/L Cerebellar Hemispheres
Vermis
L Hippocampus
L Middle Temporal Gyrus(B20)

hemispheres, medial prefrontal cortex, precuneus) (Fig. 3A). Future studies using larger numbers of subjects will be necessary to verify this finding.

In addition to the differences in functional connectivity between depressed and healthy subjects, there were some interesting differences in the direction of regional brain co-activations in the two groups. Consistent with the results of the univariate analysis (Epstein et al., 2006), a differential response to positive words occurred in the ventral striatum, a region associated with processing of reward (McGinty, 1999), positive stimuli (Phan et al., 2002) and self-relatedness (Phan et al., 2004), with healthy subjects demonstrating an increase in activation (PC 2), and depressed patients demonstrating a decrease (PC 1). A similar pattern occurred in B10, a region of dorsal medial-prefrontal cortex associated with the default mode network and self-referential mental activity, with healthy subjects again demonstrating an increase (PC 2) and depressed subjects demonstrating a decrease (PC 1) in activation. While it is difficult to determine if the B10 deactivations were driven by task performance, decreased self-referential processing, or both, these co-deactivations in ventral striatum and dorsal medial prefrontal cortex provide a possible neural substrate for impairments in positive self-related cognition seen clinically in patients with depression. This finding is in contrast to studies that demonstrate hyperactivity (failed deactivation to task) in anterior portions of the default mode network in response to negatively valenced stimuli – a difference likely related to differential propensities for negative vs. positive self-related reflection (Grimm et al., 2009a, 2009b; Sheline et al., 2009).

It is difficult to compare our findings with those reported in previous studies of functional connectivity in depression, cited above, due to differences in paradigm design (e.g., task vs. rest) and methods of analysis (e.g., region of interest, seed, ICA, PCA). As further investigations of functional connectivity are conducted in healthy and depressed subjects, it is likely that a more integrated neural network model will emerge. In addition to differences in analytic methods, our use of valenced linguistic stimuli in comparison to other emotional stimuli, including negatively valenced pictures, may account for our lack of differential findings in the negative and neutral word viewing conditions. Future studies examining neural patterns of response to a multiplicity of emotionally valenced stimuli may help clarify divergent results (Grimm et al., 2009a,b).

It must be kept in mind that functional connectivity is not synonymous with anatomic connectivity. The connection implied by a finding of intercorrelation between two regions could result from a direct anatomical and functional connection or an indirect connection through another area that affects both of the regions in question (Friston, 1994). Studies using diffusion tensor imaging in humans and retrograde tracers in animals can help answer questions of anatomic connectivity raised by such functional findings (McGinty, 1999). Other limitations of the study include the relatively small number of subjects and the unequal distributions of gender and handedness (although these did not appear to play a significant role in the results of the univariate analysis, where gender and handedness were used as covariates-of-no-interest in all between-group analyses and where findings remained in a single-sex subanalysis) (Epstein et al., 2006).

In conclusion, a principal component analysis of fMRI data collected during positive affective processing revealed that in healthy subjects, the task of viewing positive words followed by pressing a button was mediated, primarily, by functional networks involved in its sensory, linguistic and motor aspects, accompanied by anticorrelations in default mode network processing; while a distinct, secondary functional network processed the emotional content. In contrast, the same task was mediated, in depressed subjects, by a primary principal component involving functional connectivity of sensory/linguistic/motor/default mode *and* emotional networks. This finding may represent a systems level neural substrate for a core phenomenon of major depression: the interconnection of affective disturbance with experience, cognition and behavior.

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