Temporal Lobe and "Default" Hemodynamic Brain Modes Discriminate Between Schizophrenia and Bipolar Disorder

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Abstract: Schizophrenia and bipolar disorder are currently diagnosed on the basis of psychiatric symptoms and longitudinal course. The determination of a reliable, biologically-based diagnostic indicator of these diseases (a biomarker) could provide the groundwork for developing more rigorous tools for differential diagnosis and treatment assignment. Recently, methods have been used to identify distinct sets of brain regions or "spatial modes" exhibiting temporally coherent brain activity. Using functional magnetic resonance imaging (fMRI) data and a multivariate analysis method, independent component analysis, we combined the temporal lobe and the default modes to discriminate subjects with bipolar disorder, chronic schizophrenia, and healthy controls. Temporal lobe and default mode networks were reliably identified in all participants. Classification results on an independent set of individuals revealed an average sensitivity and specificity of 90 and 95%, respectively. The use of coherent brain networks such as the temporal lobe and default mode networks may provide a more reliable measure of disease state than task-correlated fMRI activity. A combination of two such hemodynamic brain networks shows promise as a biomarker for schizophrenia and bipolar disorder. *Hum Brain Mapp 29:1265–1275, 2008.*

Key words: fMRI; schizophrenia; bipolar; independent component analysis

INTRODUCTION

There is currently no diagnostic test for either schizophrenia or bipolar disorder. Both are diagnosed using cross-sectional clinical symptoms plus information on longitudinal course and outcome. It has been long recognized that there is substantial symptomatic overlap between the disorders [Kraepelin, 1921], as well as overlap in disease progression, making differential diagnosis difficult in the absence of a diagnostic "gold standard". The identification of objective, biologically-based, disease indicators or "biomarkers", is currently an active research area. Several candidates have been proposed for schizophrenia and bipolar

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disorder [Salisbury et al., 1998; Thomas et al., 2003; Tsuang et al., 2005], however, there is yet no replicable finding which has proven accurate enough for clinical decision making. The potential utility of functional magnetic resonance imaging (fMRI) in neuropsychiatry has been recognized for some time [Levin et al., 1995]. Indeed, functional and structural MRI studies have identified brain alterations in schizophrenia and bipolar disorder. However such findings to date have not provided a diagnostic classification that is both sensitive and specific.

Schizophrenia is a psychotic disorder characterized by altered perception, thought processes, and behaviors [Liddle, 1987], in which disturbed integration of neural activity or dysfunctional connectivity across multiple brain regions is considered a central feature [Friston, 1999]. Previous work has implicated abnormalities in superior temporal gyrus, mesial temporal lobe, and frontal lobe regions among other regions [Fletcher et al., 1999]. Bipolar illness is a mood disorder involving prolonged states of depression and/or mania. Studies of neurocognitive dysfunction in both illnesses indicated that persistent neurocognitive deficits may reflect underlying pathophysiology of the disorder and may, in some cases, show the characteristics of an endophenotype [Glahn et al., 2004]. The neural mechanisms underlying these deficits, however, remain unclear. Results from several studies support the hypothesis that abnormalities in ventral prefrontal cortex, ventral striatum, and limbic regions may form the neural basis for the observed deficits in bipolar disorder [Blumberg et al., 2003; Phillips et al., 2003; Yurgelun-Todd et al., 2000]. A number of studies of both behavioral and structural imaging studies have directly compared schizophrenia patients with those with various mood disorders [Pearlson et al., 1997; Strasser et al., 2005]. For example, Farrow et al. found structural deficits in lateral and medial frontal regions and in bilateral posterior temporal lobe regions in schizophrenia whereas changes in bipolar patients were localized to bilateral inferior temporal gyri with additional loss over time observed only in the anterior cingulate cortex [Farrow et al., 2005]. However there has been little work investigating functional differences between these two patient groups.

To differentiate healthy controls, schizophrenia, and bipolar disorder using fMRI it is important to identify an activation pattern which is both robust and which involves brain regions which are differentially activated in the three groups. Recent work has identified several temporally synchronous brain networks or "modes" which are present in healthy subjects either at rest [Beckmann et al., 2005; Kiviniemi et al., 2003; Van de Ven et al., 2004] or during the performance of a task [Calhoun et al., 2001b; McKeown et al., 1998]. In this article we use the words "network", "mode", and "component" interchangeably to refer to a set of regions which exhibits temporally synchronous fluctuations in fMRI activity and we focus upon two networks which have been previously studied in schizophrenia [Bluhm et al., 2007; Calhoun et al., 2004; Garrity et al., 2007). The first network includes regions in bilateral temporal lobe, which have previously been used for successful discrimination of healthy controls and schizophrenia [Calhoun et al., 2004]. A second network that includes regions used when the brain is idle, but whose activity decreases on performance of a task, is termed the "default mode network" [Raichle et al., 2001]. Together the temporal lobe and default brain modes involve many of the regions previously implicated in schizophrenia and bipolar disorder [Pearlson et al., 1996].

One of the most robust functional abnormalities in schizophrenia manifests as a decrease in the temporal lobe amplitude of the "oddball response" in event-related potential (ERP) data [McCarley et al., 1991]. Similar finding have been shown for fMRI data as well, again particularly in temporal regions [Kiehl and Liddle, 2001]. Work by Fletcher et al. replicated earlier work showing, in schizophrenia patients, a lack of deactivation of superior temporal regions which was independent of memory-task performance, possibly reflecting a core abnormality of the condition [Fletcher et al., 1998]. More recently, we reported discriminating schizophrenia from healthy control subjects with 94% accuracy using coherent temporal lobe fMRI activity [Calhoun et al., 2004]. There has been some evidence showing temporal lobe volume reductions in bipolar disorder, although the findings are less consistent than in schizophrenia [Soares and Mann, 1997; Strakowski et al., 1999; Strasser et al., 2005]. There is also some ERP work showing decreases in P300 amplitude during the auditory oddball task in bipolar disorder [O'Donnell et al., 2004]. In summary, the temporal lobe brain network appears robust, identifiable, and includes brain regions which are thought to be relevant to both disorders (perhaps more relevant to schizophrenia, but this fact may be helpful in differentiating the two diseases).

Default mode network regions are proposed to participate in an organized, baseline default mode of brain function that is diminished during specific goal-directed behaviors [Raichle et al., 2001]. The default mode network includes the posterior cingulate, medial prefrontal, parahippocampal, and inferior parietal cortices [McKiernan et al., 2003]. This network has been implicated in self referential and reflective activity including episodic memory retrieval, inner speech, mental images, emotions, and planning future events [Greicius and Menon, 2004; Mazoyer et al., 2001]. It is proposed that the default mode is involved in attending to internal versus external stimuli and is associated with the stream of consciousness, comprising a free flow of thought while the brain is not engaged in other tasks [Gusnard et al., 2001]. There has been evidence implicating parietal and cingulate regions in both bipolar disorder and schizophrenia [Benes et al., 2001; Hasler et al., 2006; Kiehl and Liddle, 2001; Pearlson et al., 1997; Thomas et al., 2003]. We and others have recently shown differences in the default mode in patients with schizophrenia [Bluhm et al., 2007; Garrity et al., 2007; Williamson, 2007].

In this work, we extracted the temporal lobe and default brain modes from fMRI data during the performance of an

TABLE I. Demographic and clinical characteristics of patients with schizophrenia (n = 21), patients with bipolar disorder (n = 14), and matched healthy controls (n = 26)

Variable	SZ	BP	HC	t/P-value (HC/SZ)	t/P-value (HC/BP)	t/P-value (SZ/BP)
Age	34.9 ± 11.8	33.2 ± 9.9	30.3 ± 8.8	NS	NS	NS
Percent male	71	72	73	NS	NS	NS
NART, estimated IQ	107.6 ± 12.1	108.8 ± 8.3	118.5 ± 5.5	3.9/0.0002	4.6/0.0001	NS
Quick test correct	43.3 ± 3.8	43.8 ± 2.7	45.5 ± 2.2	2.3/0.02	2.3/0.02	NS
Duration of illness (years)	12.4 ± 11.7	16.3 ± 10.1	NA	NA	NA	NS
Onset of Illness (age)	21.2 ± 5.3	24.1 ± 13.5	NA	NA	NA	NS
Percent treated with atypical antipsychotic medication	100	72	NA	NA	NA	NA
Percent treated with antidepressants	34	91	NA	NA	NA	NA
Percent with some psychotic symptoms	86	29	NA	NA	NA	NA

SZ, schizophrenia; BP, bipolar; HC, healthy control; NS, nonsignificant; NART, National adult reading test; NA, nonapplicable. Group comparisons are reported in the three columns at the right.

auditory oddball task [Calhoun et al., 2004]. Both networks are readily (and unambiguously) identified using independent component analysis (ICA) [Beckmann et al., 2005; Kiviniemi et al., 2003; Van de Ven et al., 2004]. These two networks were selected (to the exclusion of other, less well understood networks) because both have been previously studied [Calhoun et al., 2004; Greicius et al., 2003; Raichle et al., 2001] and both involve brain regions which are known to be implicated in schizophrenia [Bluhm et al., 2007; Calhoun et al., 2004; Garrity et al., 2007; Starck et al., 2006]. In its application to fMRI, ICA separates the image data into a set of spatially distinct networks and their temporal signatures [Calhoun et al., 2001a; McKeown et al., 1998]. In this work, we used the auditory oddball task both as a way to have more control over participant's behavior beyond just "resting" and also to stimulate the brain with a task that both patients and controls can perform accurately and which is known to elicit robust brain function differences between the two groups [Kiehl and Liddle, 2001; Kiehl et al., 2005b; Salisbury et al., 1998].

We hypothesized that incorporating the temporal lobe and default mode networks into a classification algorithm would provide reliable discrimination criteria for schizophrenia, bipolar disorder, and healthy controls. We used ICA to calculate the spatially independent brain modes, and we selected the temporal lobe and default mode networks for each participant. We then combined the spatial maps and developed a classifier using a leave-one-out approach, thus classifying an independent set of participants in order to validate the result.

MATERIALS AND METHODS

Participants

Participants consisted of 26 healthy controls, 21 chronic schizophrenia outpatients, and 14 bipolar Type I outpatients, all of whom gave written, informed, IRB approved consent at Hartford Hospital and were compensated for their participation. A portion of the healthy control and schizophrenia data were reported on in a previous work [Kiehl et al., 2005b]. Schizophrenia or bipolar disorder was diagnosed according to the criteria in the DSM-IV on the basis of a structured clinical interview administered by a research nurse and review of the medical file [First et al., 1995]. Exclusion criteria included any participants with auditory or visual impairment, mental retardation (full scale IQ < 70), traumatic brain injury with loss of consciousness greater than 15 min, presence or history of any neurological illness. Participants were also excluded if they met criteria for alcohol or drug dependence within the past 6 months or produced a positive (assessed by urine toxicology screen on the day of scanning). Seventeen schizophrenia patients were receiving stable treatment with atypical antipsychotic medications [quetiapine (4), aripiprazole (1), olanzapine (5), risperidone (4), clozapine (3)] and nine patients were on antidepressants. Eight of the bipolar patients were on atypical antipsychotics [quetiapine (6), aripiprazole (1)] and 10 were on antidepressants, one bipolar patient was on lithium, three were on anticonvulsants. Medication information was not available for four schizophrenia patients and three bipolar patients. All participants were right handed, had normal hearing, and were able to perform the oddball task successfully during practice prior to the scanning session. Healthy participants were free of any DSM-IV Axis I disorder or psychotropic medication. The National Adult Reading Test was employed to estimate premorbid intelligence [Nelson and O'Connell, 1978] and the Quick Test was used to estimate current intellectual functioning [Ammons and Ammons, 1962]. All assessments were performed by individuals blind to the fMRI findings. Demographic and clinical characteristics are reported in Table I.

Experimental Design

Two runs of 244 stimuli were presented to the participant using a custom presentation package (http://nilab.psychiatry.ubc.ca/vapp/) and an MRI compatible sound system (Magnacoustics). The stimuli consisted of nontarget

stimuli (1-kHz tones, 75% probability), target stimuli (1.5-kHz tones, 12.5% probability), and nonrepeating random digital noises (e.g., tone sweeps, whistles, 12.5% probability). The stimulus duration was 200 ms with a 1,800 ms interstimulus interval. Participants were instructed to respond as quickly and accurately as possible with their right index finger every time the target tone occurred and not to response to nontarget tones or novel stimuli. An MRI compatible fiber-optic response device (Lightwave Medical, Vancouver, BC) was used to acquire behavioral responses in all studies. Prior to entry into the scanning room, each participant performed a practice block of 10 trials. The stimulus paradigm data acquisition techniques and stimulus-related activation are described more fully in [Kiehl et al., 2005a].

Image Acquisition

Scans were acquired at Hartford Hospital on a GE 1.5 Tesla scanner. Functional scans consisting of two runs of gradient-echo echo-planar scans (TR = 3 s, TE = 40 ms, field of view = 24 cm, matrix = 64 × 64, slice thickness = 5 mm, gap = 0.5 mm, 29 slices) were obtained consistently over an 8-min 20-s period for a total of 167 scans per run. Four "dummy" scans were performed at the beginning to allow for longitudinal equilibrium.

Preprocessing

Data were preprocessed using the SPM2 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). Data were motion corrected, spatially smoothed with a 10 mm^3 full width at half-maximum Gaussian kernel, spatially normalized into the standard Montreal Neurological Institute space, and then coordinates were converted to the standard space of Talairach and Tournoux [Talairach and Tournoux, 1988]. During spatial normalization, the data (acquired at 3.75 × 3.75 × 5.5 mm^3) were resampled to 4 mm^3, resulting in 40 × 48 × 34 voxels. Group spatial ICA [Calhoun et al., 2001a] was used to decompose all the data into 25 components using the GIFT software (http://icatb.sourceforge.net/) as follows. Dimension estimation, to determine the number of components, was performed using the minimum description length criteria, modified to account for spatial correlation [Li et al., in press]. Data from all subjects were then concatenated and this aggregate data set reduced to 25 temporal dimensions using PCA, followed by an independent component estimation using the infomax algorithm [Bell and Sejnowski, 1995].

Creation of Spatial Maps and Time Courses

For each participant, spatial maps were then reconstructed and converted to Z values, hence the intensities of the image provide a relative strength of the degree to which the component contributes to the data [Beckmann et al., 2005]. The default mode and temporal lobe components were identified in a fully automated manner by spatially sorting the components in GIFT using masks derived from the wake forest university pick atlas (http://www.fmri.wfubmc.edu/download.htm). For the temporal lobe mask we used Brodmann areas 20, 21, 22, 37, 38, and 42 and for the default mode mask we used precuneus, posterior cingulate, and Brodmann areas 7, 10, and 39 [Correa et al., 2007]. A spatial multiple regression of the masks with each of the components is performed, and the component which has the best fit with each of the two masks is automatically selected as the temporal lobe and default mode components. A voxel-wise one-sample t-test was computed for each group and both components (this treats each subject as a random effect and hence provides a statistical threshold on the maps) [Calhoun et al., 2001a]. Results are shown in Figure 1 and thresholded at $P < 0.001$ (corrected for multiple comparisons). To compute the degree of task-relatedness of the brain mode time courses, regressors modeling the target and novel stimuli were created (calculated by convolving the ideal timing of the events with a canonical hemodynamic response function) using the SPM2 software. These regressors were fit to the calibrated time courses for each individual using GIFT and the average percent signal change was computed for each group.

Classification

Once the two brain modes were identified for each individual, a multistage classification algorithm was developed. First, the temporal lobe and default brain mode images were concatenated into a single image for each participant. Voxels from the entire brain were initially included in the algorithm. An adaptive threshold was then used to select a subset of the voxels which minimized the total classification error. A mean image was computed for each group, and the Euclidean distance between an individual's brain image and each group's images was computed. A given image was classified as belonging to a group if the distance to that image was less than that to the other two groups. To validate the classification procedure, a leave-one-out approach was used in which one participant from each group was randomly excluded, the classifier was developed on the remaining participants, and the left-out subjects were then classified (these are the ones shown in Fig. 3) and the process was repeated. The detailed algorithm is as follows:

1. Define leave-one-out groups as g_{schizo}, g_{bipo}, g_{cont} by removing one randomly selected participant from each group
2. Concatenate both brain modes into a single image
3. Compute group average and voxel-wise one-sample t-test images μ_{schizo}, μ_{bipo}, μ_{cont} and t_{schizo}, t_{bipo}, t_{cont}
4. Compute pair-wise difference images $d_{cont\text{-}schizo} = \mu_{cont} - \mu_{schizo}$, $d_{cont\text{-}bipo} = \mu_{cont} - \mu_{bipo}$, $d_{schizo\text{-}bipo} = \mu_{schizo} - \mu_{bipo}$
5. Select random threshold from uniform distribution $t_1 \in [0,2]$

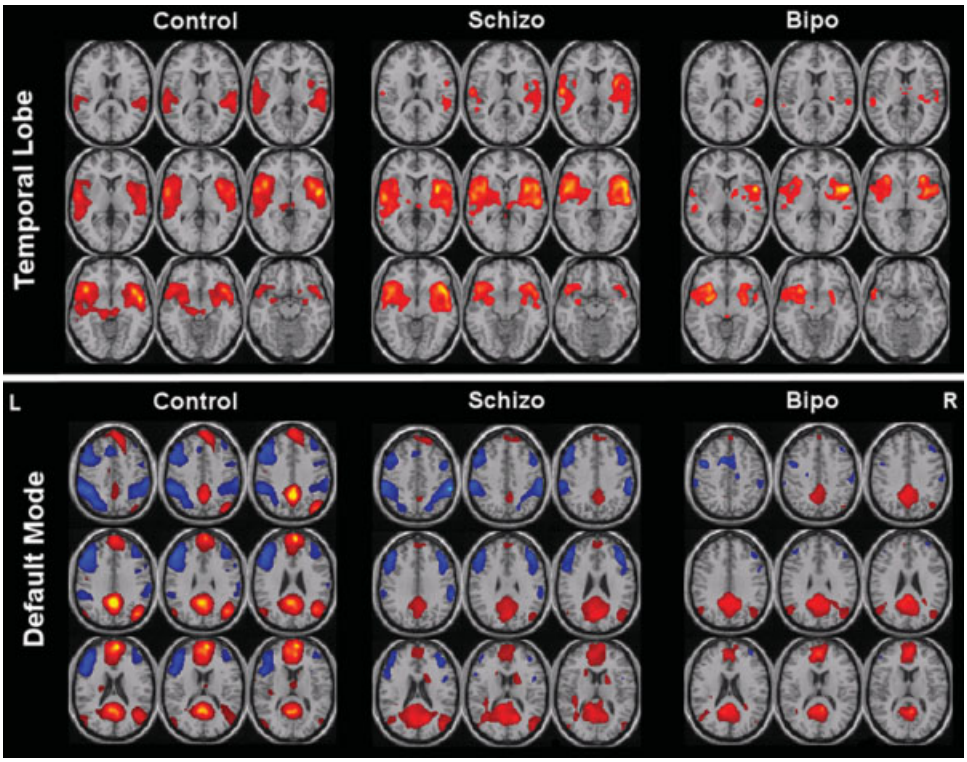

Figure 1.
Temporal lobe and default mode components. Group average temporal lobe (top) and default mode (bottom) features, extracted from fMRI data for controls, schizophrenia patients, and bipolar patients, thresholded at $P < 0.001$ (corrected).

6. For each pair-wise difference $\delta \in$ {cont-schizo, cont-bipo, schizo-bipo}
   (a) select random threshold μ_+, $\mu_- \in$ [0, 0, 0.5, 0.5, 1, 1, inf] sampled without replacement
   (b) select voxels v_δ which satisfy $\{\delta > \mu_+ \cup \delta < \mu_-\}$ and $\{t_{schizo} > t_1 \cup t_{bipo} > t_1 \cup t_{cont} > t_1\}$ (where $\cup$ represents the union of two sets)
7. For each participant (excluding those left out in step 1), and for each group
   (c) Compute Euclidean distance $D_{g,p}$ between group mean voxels and participant voxels
   (d) Classify as cont if $D_{cont,i} > D_{schizo,i}$ and $D_{cont,i} > D_{bipo,i}$, $D_{schizo,i} > D_{cont,i}$ and $D_{schizo,i} > D_{bipo,i}$, bipo if $D_{bipo,i} > D_{cont,i}$ and $D_{bipo,i} > D_{schizo,i}$
8. Compute sum of all false positive and false negative classification errors
9. Repeat steps 5–8 until error is minimized

Once the classifier is developed, we then classify the remaining subjects as follows:

10. For each of the three left-out participants
    (e) Compute Euclidean distance $D_{g,p}$ between group mean voxels from step 7a and each participant's voxels
    (f) Classify as cont if $D_{cont,i} > D_{schizo,i}$ and $D_{cont,i} > D_{bipo,i}$, schizo if $D_{schizo,i} > D_{cont,i}$ and $D_{schizo,i} > D_{bipo,i}$, bipo if $D_{bipo,i} > D_{cont,i}$ and $D_{bipo,i} > D_{schizo,i}$
11. Return to step 1 and repeat

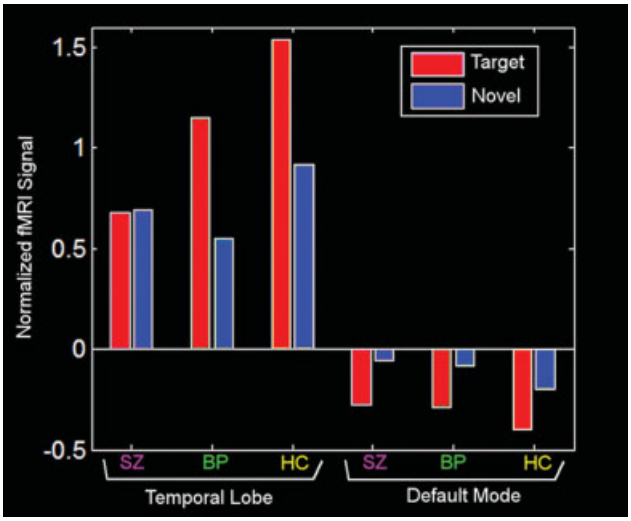

Figure 2.
Task-relatedness of temporal lobe and default mode maps. Degree to which the temporal lobe (left) and default mode (right) component time courses were associated with the presented stimuli for schizophrenia (SZ), bipolar disorder (BP), or healthy controls (HC). The temporal lobe component was positively fluctuating with the task, with healthy controls the highest, then bipolar, then schizophrenia. The default mode was negatively fluctuating with the task and showed the same ordering of absolute magnitude for the groups.

TABLE II. Behavioral results

Variable	SZ	BP	HC
Correct hits (%) (mean ± standard deviation)	98.3 ± 2.4	99.0 ± 3.0	99.1 ± 1.6
Errors of omission (%)	1.7 ± 2.4	1.0 ± 3.0	0.9 ± 1.6
Errors of commission (%)	5.3 ± 6.1	4.5 ± 6.3	3.9 ± 6.3
Reaction times (ms)	496 ± 124	496 ± 139	437 ± 95

SZ, schizophrenia; BP, bipolar; HC, healthy control; NS, nonsignificant. Correct response, errors, and reaction times for the auditory oddball task. For all behavioral measures tested group comparisons did not reach significance at the $P < 0.05$ level.

RESULTS

Behavioral results showed no significant differences between groups for reaction time, correct hits, errors of omission, or errors of commission (Table II). Consistent with previous findings [Kiehl and Liddle, 2001], healthy controls responded to target stimuli slightly faster than did either schizophrenia or bipolar patients although this did not reach conventional levels of statistical significance ($P < 0.07$).

Average maps for the temporal lobe and default mode components are presented in Figure 1 for healthy controls (left), patients with schizophrenia (middle), and patients with bipolar disorder (right). A qualitative comparison suggests different brain regions exhibit different patterns within each group. For example, default mode maps from healthy controls show lateral frontal and parietal decreases (blue regions), not present in the bipolar group, which is characterized by decreases in cingulate cortex. Likewise, schizophrenia and bipolar patients exhibit moderate increases in posterior cingulate and bilateral parietal lobe, whereas controls show maximal changes in these regions. Temporal lobe maps largely reveal positive (orange) regions, with bipolar patients having a focal maximum in anterior temporal lobe, whereas control patterns are much more diffuse. In general, it appears that these images provide evidence of overlapping and distinct patterns of synchronous neural activity in the three diagnostically separate groups.

Because these brain modes are estimated from data collected during the performance of an auditory oddball task, we examined the degree to which their behavior in time was task-related (see Fig. 2). As expected, the temporal lobe component (overall $R^2 = 0.10$) increased in response to the task stimuli. In general, for target stimuli, healthy controls showed the greatest response (in units of relative percent signal change), followed by bipolar patients, then schizophrenia patients. The default mode component (overall $R^2 = 0.08$) decreased in response to the task engagement with healthy controls revealing the greatest reduction and schizophrenia and bipolar patients show similar but attenuated reductions.

Our primary goal was to determine the degree to which the spatial maps for temporal lobe and default mode maps discriminated the three groups. We developed a three-way classification algorithm by computing the Euclidean distance of a given individual's temporal lobe and default mode map to each group's average map. The classified individual was *not* included in the group average maps, nor was this individual used to optimize the thresholds (for details see methods section). In this way, the performance of the classifier on an independent data set was computed. Figure 3 reports results for each comparison (a) control versus noncontrol, (b) schizophrenia versus nonschizophrenia, (c) bipolar versus nonbipolar along with the a priori decision regions used for each group; control (dark yellow), schizophrenia (dark pink), and bipolar disorder (dark green). Each dot represents an individual and the color of the dot indicates the true diagnosis of healthy (yellow), schizophrenia (pink), or bipolar disorder (green).

Results show a high average sensitivity (90%) and specificity (95%). Controls were correctly classified 95% of the time, schizophrenia patients 92%, and bipolar patients 83%. A breakdown of sensitivity and specificity for each group is shown in Figure 3.

We can also do a more direct subtractive comparison of each of the three groups using three two-sample *t*-tests. Figure 4 shows the results from these comparisons thresholded at $P < 0.025$ (uncorrected) and is consistent with what was shown in the maps in Figure 1. Both temporal lobe and default mode maps appear to be contributing in different ways to the classification of each group. Anterior temporal lobe regions have larger component voxel values in controls versus schizophrenia and bipolar patients whereas posterior temporal lobe regions have larger component voxel values in bipolar patients versus controls and schizophrenia patients. In the default mode, bipolar patients have decreased (positive task-related) activity in lateral frontal regions compared with both schizophrenia patients and controls, whereas schizophrenia patients are showing more (negative task-related) activity in posterior cingulate and parietal regions. Note that the average map includes all subjects, so the classification results will use slightly different regions since the subject being classified is always left out of the average map.

Analysis of Medication, Group, and Symptoms

A multivariate analysis of variance (MANOVA) was conducted to examine whether relationships between metrics used to classify individuals ($D_{cont,i} - D_{schizo,i}$, $D_{cont,i} - D_{bipo,i}$, $D_{schizo,i} - D_{bipo,i}$) and group membership (schizophrenia, bipolar) were confounded with antipsychotic medication, antidepressant medication, or psychotic symptoms in the two patient groups ($N = 22$). In this analysis, we found that only group membership was significantly associated with the metrics used to perform the classification (Wilks' Lambda = 0.489; $F = 5.23$, df1 = 3, df2 = 15,

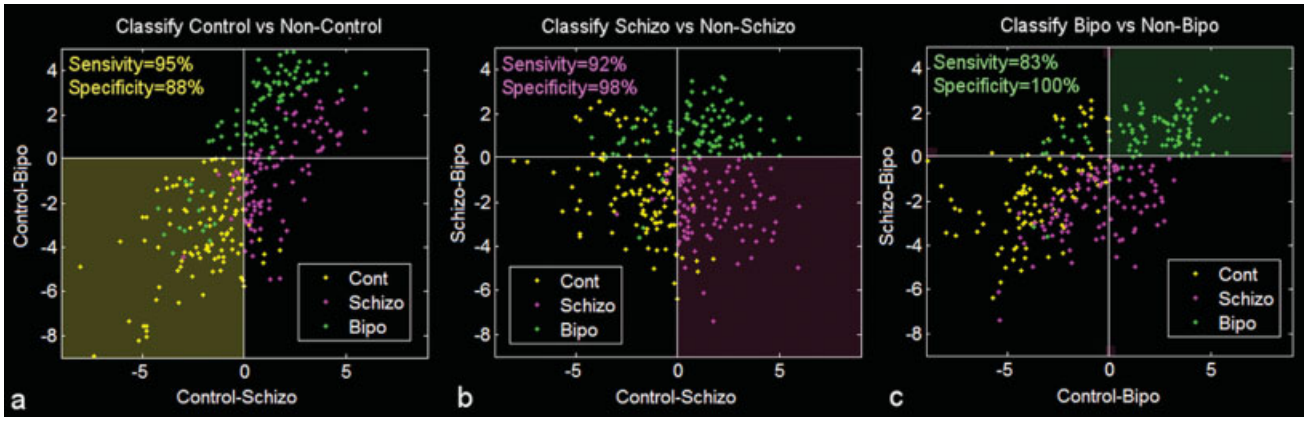

Figure 3.

Classification results. A priori decision regions for three-way classification for (**a**) control (dark yellow) versus noncontrol (black), (**b**) schizophrenia (dark pink) versus nonschizophrenia (black), and (**c**) bipolar (dark green) versus nonbipolar (black). The actual diagnosis of a given individual is indicated by the color of the dot where controls are yellow, schizophrenia patients are pink, and bipolar patients are green. The classification was done on an independent data set each time using a leave-one-out approach. Sensitivity and specificity values were quite encouraging, with an average sensitivity of 90% and an average specificity of 95%.

$P = 0.011$). Within the context of this analysis, we found no significant associations between these metrics and antipsychotic medication (Wilks' Lambda = 0.840; $F = 0.96$, df1 = 3, df2 = 15, $P = 0.439$), antidepressant medication (Wilks' Lambda = 0.808; $F = 1.19$, df1 = 3, df2 = 15, $P = 0.348$), and psychotic symptoms (Wilks' Lambda = 0.832; $F = 1.01$, df1 = 3, df2 = 15, $P = 0.415$). The results of this MANOVA suggest that the main results of our study are neither confounded with, nor significantly biased by, these factors.

Robustness of ICA and GLM Maps

Because the robustness of the extracted activation maps or components is a critical factor in classification accuracy we were interested in how consistent the estimated networks were in our data. Later we provide preliminary evidence that the networks identified with ICA are more consistent than the activation maps determined using a conventional analysis. For an auditory oddball task we computed target-related activation maps using a standard general linear model (GLM) analysis and extracted the temporal lobe mode from an IC analysis. Figure 5 shows maps computed from as few as 49 time points up to 167 time points. The ICA results shows considerably more consistency than the GLM results. This is also quantified by performing a spatial correlation of each result with the image computed from 167 time points (correlation values shown in the right side of Fig. 5). Results in Figure 5 are from a representative subject, but are the same for a group analysis and suggest that the spatial maps produced by ICA may be more robust than those produced by the GLM.

Posthoc Inclusion of Additional Networks

In general it appears that the temporal lobe and default mode networks contribute differently. The temporal lobe does a better job in separating the patients with chronic schizophrenia from healthy controls; however the default mode maps provide a better separation between the bipolar patients and the other two groups. In addition to the

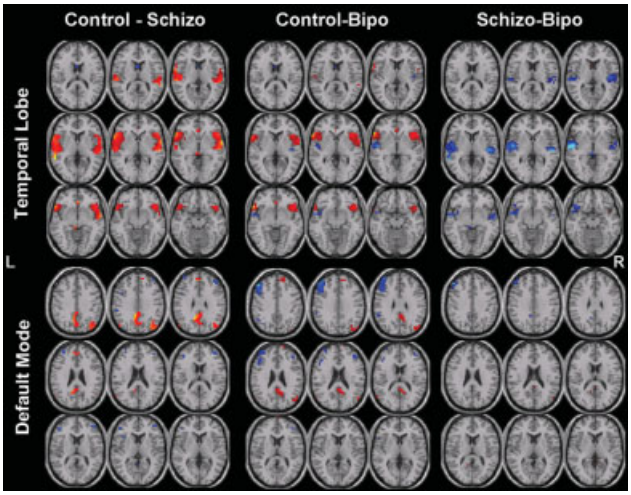

Figure 4.

Pair-wise comparisons of the control, schizophrenia, and bipolar groups. Two-sample *t*-tests were performed to illustrate most significant differences for each pair-wise comparison. Note that these maps are generated from all subjects and actual classification regions will be slightly different due to the leave-1-out approach.

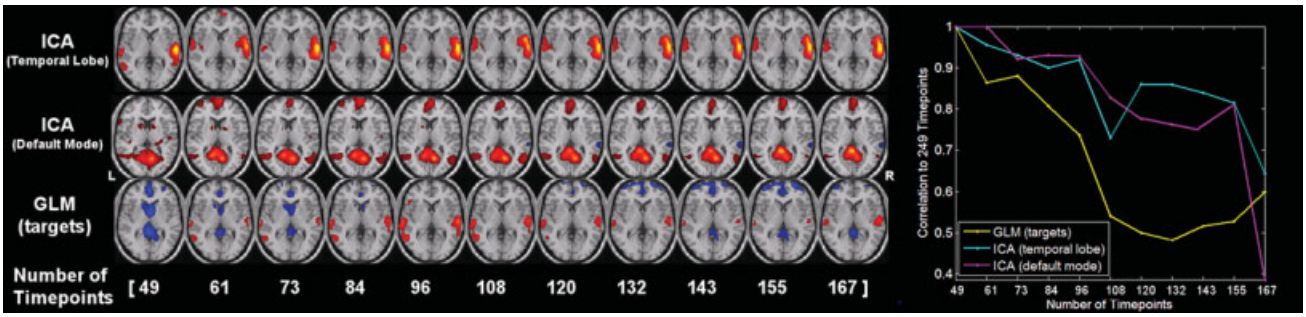

Figure 5.

Consistency of ICA and GLM maps. ICA temporal lobe component (top left), ICA default mode component (middle left), and GLM target-related (bottom left) maps created using a subset of data ranging from 49 to 167 time points. The ICA maps appear to be more consistent even for a very small subset of the data. Spatial correlation of the "best" image (that resulting from 167 time points) with all the other images (right) reveals a higher consistency than the GLM in almost all cases.

above analyses, we examined whether there was a benefit to including additional ICA networks in the classification algorithm. We manually selected eight networks, including default mode and temporal lobe, which appeared to be blood oxygen-level dependent-related (i.e., they showed no edge effects, were not prominently located in ventricles or white matter, and were focal and localized to gray matter). When we reran the classification algorithm, again using a leave-one-out approach, the sensitivity and specificity were the same as they were in our primary reported analyses results. We also computed a histogram of patient versus control differences and we found that the default mode has the most voxels (eight times as many as the next network) followed next by the temporal lobe and the other networks. Though it is possible that the other networks may prove beneficial for classification in general, for the classification approach used in this study—which was intentionally designed to have a minimum of parameters to avoid the problem of overlearning—there was no additional benefit.

DISCUSSION

While the development of objective classification algorithms for clinical diagnostic decision-making in psychiatry is an attractive goal, such efforts have been hampered by the transient and subjective nature of self-reported symptoms, as well as the large overlap in phenomenology and course between traditional patient groupings, often leading to poor diagnostic sensitivity or specificity. A recent survey of diagnostic tools for bipolar disorder shows that a clinician's estimate of prior probability (i.e., assumptions of disease prevalence) has a large impact on the clinical performance of standard survey tools [Phelps and Ghaemi, 2006]. The sensitivity of the tests examined ranged from 28 to 73% whereas the specificity was from 67 to 90%. The incorporation of additional biomarkers such as electroencephalographic [Salisbury et al., 1998], genetics [Tsuang et al., 2005], and neurochemistry [Thomas et al., 2003] has been used preliminarily to distinguish bipolar disorder from schizophrenia with some success [Hasler et al., 2006]. Biomarkers have the potential to improve sensitivity and specificity by incorporating additional data which may be less variable (or more predictive of change) than clinical symptoms, which typically need to be combined with outcome data tracked over a period of months in order to develop an accurate diagnosis. To our knowledge there has been no published work which attempts to perform a three-way classification using fMRI imaging data in the disorders we studied.

Our approach attempts to overcome several challenges associated with the use of brain imaging to study mental illness. First, fMRI results involving bipolar disorder and schizophrenia suffer from large variability and low robustness. The use of coherent brain networks may well prove to be more consistent and robust. Secondly, when complex cognitive tasks are used, performance deficits can confound activation patterns (and may contribute to some of the interparticipant variability). The current study attempted to mitigate this problem by identifying temporally coherent brain networks and employing a task in which patients perform almost as well as controls. The use of resting-state fMRI data may provide a way to remove the element of task performance completely; however the resting condition is largely uncontrolled and may induce confounding variation of its own. We show that, using a combination of two distinct brain networks derived from fMRI data, high sensitivity and specificity for a three-way classification can be obtained.

In our analysis, the number of components is fixed for each subject to be the same. While it is possible that the dimensionality of the patients and controls could be different, we selected the approach we used for several reasons. First, a change in the number of components by a small degree (5–10) does not appear to change the pattern of activity in each map (results not shown). Secondly, if we fix

the dimensionality this makes the approach easier to apply for possible diagnostic purposes. We do not believe the dimensionality should be a free parameter, since existing methods for estimating dimensionality do not always work well for a variety of reasons. Thus we would, based upon this work, suggest fixing the dimensionality to 25, and estimating the IC maps from the subjects to be classified.

Though there has been little work looking at differences in the default mode and temporal lobe independent components in bipolar disorder and schizophrenia, the regions contributing to the classification are consistent with previous findings. Temporal lobe regions are known to show diminished activation in patients with schizophrenia [Kiehl and Liddle, 2001; Kiehl et al., 2005b], and also ERP studies have shown differences in the P300 response in bipolar disorder and schizophrenia [O'Donnell et al., 2004]. Structural MRI has shown consistent temporal lobe abnormalities in schizophrenia, but the results in bipolar disorder are less consistent [Soares and Mann, 1997; Strakowski et al., 1999]. Both networks showed less task-related activity in both bipolar disorder and schizophrenia (see Fig. 2). Both patient groups show some regions which have larger component voxel values than controls and others which show smaller component voxels values than controls. This suggests that networks identified with multivariate methods such as ICA may shed new light on currently held views of functional (dis)connectivity in mental illness. The contribution of the two studied networks to the classification also appears to be somewhat different for the different patients groups. Qualitatively it appears default mode (in particular the lateral frontal areas) appear to be slightly more useful for distinguishing the bipolar patients whereas temporal lobe is more useful for the schizophrenia patients (although both network are contributing to the classification to varying degrees). This makes sense if one considers the default mode network contains cingulate regions, which have been shown in some studies to be differentially affected in bipolar disorder [Bouras et al., 2001]. It has also been shown in various studies that superior temporal gyrus is more affected in schizophrenia [Pearlson, 1997].

The determination of biologically-based criteria for the determination of schizophrenia or bipolar disorder would be a major step forward. Computational approaches play an important role in distilling the large amount of data that can be collected. The use of genetic information to develop a "blood test", though relevant, is not necessarily going to be successful using genetic information alone since the genetic effect of schizophrenia, for example, is thought to be modest [Cardno et al., 1999]. However, there may well be additional improvements to be gained by combining an fMRI biomarker with genetic data.

A limitation of the current study is that all patients were on psychotropic medication at the time of testing. It is possible that long-term neuroleptic exposure could produce changes in the temporal lobe and default mode maps. The impact of the psychotropic medications could artificially enhance our ability to classify patients from healthy controls (by simply changing the brain hemodynamic activity in a systematic manner). However, the high classification accuracy obtained combined with the fact that there were some bipolar patients and schizophrenia patients on the same medications, who were successfully differentiated, suggests that this is not a dominant effect. It is likely there are some features of the brain networks we explored which are consistent or *trait-related* between groups and some which are *state-related* or dependent upon the phase of the illness and other factors such as medication [Blumberg et al., 2003]. Future work will be needed to determine to what degree the state/trait changes impact functional classification. These questions are certainly critical ones needing further study, however, the fact that we are able to perform a three-way classification with high sensitivity and specificity suggests the use of multiple coherent brain networks is promising and may lead to the development of a reliable biologically-based biomarker for multiple mental illnesses. In addition, though for this study we chose to focus upon two previously studied brain modes, the incorporation of additional brain modes and different fMRI tasks may further improve results.

The patients in this study were scanned after they had been successfully diagnosed. Though one of the motivations for identifying an imaging as a biomarker of schizophrenia is that there is not yet a biological gold standard, this is also a limitation since we are ultimately comparing with the clinical findings. However, there are a number of ways an imaging biomarker can prove useful even so. One would first need to extend the current study by studying patients who have not yet been clinically differentiated as having schizophrenia or bipolar disorder. If our approach, or another like it, can differentiate bipolar disorder from schizophrenia early on, this by itself would be an advance. Imaging biomarkers can also prove useful for the prediction of treatment response or response to therapy. The current study is encouraging but additional studies are needed to exploit the full advantage of imaging as a clinical tool.

In summary, we developed a three-way classifier based upon two coherent brain "modes", the temporal lobe [Calhoun et al., 2004] and default mode [Raichle et al., 2001]. An average sensitivity of 90% and specificity of 95% was obtained providing evidence that by combining multiple functional brain modes, we may be able to differentiate two major psychiatric illnesses. The above results are encouraging given the difficulties in distinguishing bipolar patients from schizophrenia patients using symptom assessments alone.

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