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Original Article

A functional magnetic resonance imaging study of cortical asymmetry in bipolar disorder

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Objectives: Individuals with bipolar disorder (BPD) exhibit motor, perceptual, and cognitive disturbances involving predominantly right hemisphere dysfunction. This asymmetry has been used to advance the hypothesis that the pathogenesis of bipolar disorder may be related to disturbances of the right cerebral hemisphere. We employed functional magnetic resonance imaging to examine hemispheric asymmetries in manic and depressed BPD. A secondary goal of the study was to examine effects of psychotropic medications on blood volume changes in the motor cortices.

Methods: We studied 18 right-handed BPD and 13 right-handed normal healthy comparison subjects. Blood oxygen level dependent (BOLD) responses in the primary motor area (M1) and supplementary motor area (SMA) of both hemispheres were elicited during reaction time (RT) tasks.

Results: Healthy subjects activated the SMA in a reciprocal fashion with significantly greater activity in the left SMA for right hand trials and the right SMA for left hand trials. Depressed BPD subjects failed to show this normal reciprocity indicating a failure to suppress unwanted activity in the ipsilateral right SMA, whereas manic BPD subjects failed to suppress unwanted ipsilateral SMA activity in both hemispheres. Manic and depressed BPD subjects exhibited greater activity in the left primary motor area suggesting increased cortical excitability. BPD subjects treated with antipsychotics or mood-stabilizing medications exhibited longer RTs, lower BOLD responses in M1 and SMA, and a loss of normal hemispheric asymmetry in the SMA than untreated subjects.

Conclusions: The presence of a right hemisphere disturbance in BPD is consistent with the hypothesis that the right hemisphere may be dominant in mood regulation. The presence of both left and right hemisphere disturbances in mania may explain the coexisting psychotic and affective symptoms observed in this condition.

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There is compelling evidence supporting abnormal hemispheric asymmetries in the major psychotic disorders (1–3). In general, psychophysiological (4, 5), neuroimaging (6, 7), and neuropsychological (8, 5) findings demonstrate a predominant left hemisphere disturbance in schizophrenia. The findings for bipolar disorder (BPD) are less clear. Goodwin and Jamison (9), in their review of neuropsychological, dichotic listening, and other studies of laterality in manic-depressive illness, concluded, 'In general, the studies reviewed...suggest that relative functional deficits in the

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non-dominant (generally right) hemisphere can be found in both phases of manic-depressive illness' (p. 510). While electrophysiologic studies support this conclusion (10, 11), functional neuroimaging studies of hemispheric asymmetry in BPD are mixed (12–15). For example, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies show greater activity in the right than left hemisphere activity in the basal ganglia (16), temporal lobes (17, 18), and amygdala (17) in manic subjects, premotor and parietal areas in euthymic subjects (19) and in the amygdala and insula in depressed subjects (20). Yet, there are PET and SPECT studies showing greater activity in the left than right hemisphere in the temporal lobes (21), frontal (22) and prefrontal areas (23), and the cingulate cortex (24) in manic subjects and in the amygdala (25) and frontal lobe (20) in depressed subjects. Interestingly, two studies reported opposite hemispheric asymmetries in the same regions of the brain in the same subjects (19, 20).

To our knowledge, none of the functional neuroimaging studies of hemispheric asymmetry in BPD published to date involved magnetic resonance imaging (MRI). Morever, with only one exception, the PET and SPECT studies were conducted with the subjects resting. The exception was a study by Berns and colleagues (19) in which euthymic subjects performed a novel finger movement task designed to examine blood flow changes occurring during learning of serial reaction time (RT) movements. These investigators found increased regional cerebral blood flow (rCBF) in the right premotor cortex, right insular cortex, and medial prefrontal cortex and reduced rCBF in the right supplementary motor area (SMA), right superior parietal lobe and left parahippocampal region relative to healthy comparison subjects. The absence of a consistent increase or decrease in activity relative to controls is not surprising considering the euthymic nature of their subject at the time of the scan. The authors did not report which hand was used to perform the motor task; however the abnormalities involved the right motor cortical areas. If the dominant right hand was used, then the results suggest an ipsilateral motor cortical abnormality.

The findings by Berns et al. are consistent with previous studies from our laboratory. In these studies, we reported an abnormal asymmetry on an instrumental measure of force steadiness in bipolar mania implicating the right hemisphere (26, 27). However, because we did not perform an imaging study, we could not localize the particular cortical region or regions involved in this asymmetry. There are sufficient differences between the Berns et al. PET study showing right motor cortical hemisphere abnormalities in BPD (19) and our previous work on motor asymmetries in BPD (26, 27) to warrant further study. First, Berns et al. studied euthymic patients, whereas we studied manic patients. So it is not clear whether right hemisphere abnormalities are present in BPD in general, or if they are specific to a particular mood state. Secondly, Berns et al. employed a bimanual RT task in their PET study, whereas our laboratory studies involved unimanual measures of force steadiness. Because we examine one hand at a time, we were able to demonstrate the presence of abnormal hemispheric asymmetries in our bipolar manic subjects. It is difficult to interpret the Berns et al. study because it is not clear what the normal hemispheric pattern is during bimanual motor performance.

The Berns et al. study was the first to use functional neuroimaging to identify a right hemisphere abnormality in BPD patients performing a motor task. Previous functional neuroimaging studies did not involve active behavior on the part of the subjects. What remains uncertain, however, is whether the abnormalities observed by Berns et al. were consistent with what is known about the roles of the motor cortices during movement. There have been several functional neuroimaging studies of healthy individuals that serve as a guide to understanding normal hemispheric asymmetry. For example, investigators have shown that the left hemisphere primary motor cortex is more dominant than the right hemisphere for tasks involving sequential movements, (28) and task novelty (29). The left SMA is thought to be more involved in choice RT (CRT) tasks and less involved in simple RT (SRT) tasks (30). The right hemisphere motor cortical areas are more involved than the left hemisphere for motor tasks involving timing (31). Thus, the pattern of dominance of the motor cortices appears to be task specific with the left hemisphere dominating for tasks involving sequential, choice, or novel movements; whereas the right hemisphere appears dominant for tasks that depend on accurate timing. With regard to the results from the Berns et al. study, the decrease in right SMA is consistent with a disturbance in the timing of the RT sequence and/or use of visual information associated with learning a motor task. The absence of any left hemisphere abnormality suggests normal processing of sequential information.

The purpose of the present study was to elucidate further the role of the right hemisphere during motor behavior in BPD. Previous PET (19) and laboratory studies (26, 27) give ample reasons to

suspect preferential abnormalities in the right compared with the left hemisphere in BPD. The use of a motor task to study hemispheric asymmetries offers an opportunity to confirm the findings of previous PET motor study in BPD and to fill in gaps about hemispheric asymmetries in mania and depression. A great deal is known about how motor behavior is organized in terms of underlying neural structures, so we are not blind as to where to look for differences in motor cortical activity. Moreover, because of the overlap in frontal-subcortical circuits regulating motor and limbic behavior (32, 33), findings from a study of the neuromotor system can inform us about the limbic system and how these circuits may regulate mood.

In the present study, we employed functional magnetic resonance imaging (fMRI) to examine differences in hemispheric activation between manic and depressed BPD patients and between a group of normal healthy individuals during a simple and choice RT task. We designed the study design to allow an examination of the effects of hand dominance, affective state, and task complexity on asymmetries in motor cortical activity. With this design, we hoped to resolve many questions stemming from previous studies. Consistent with our previous laboratory motor studies (26, 27) and a previous PET study of RT in BPD, we hypothesized that manic and depressed BPD subjects would exhibit abnormalities in the cortical activation of the right hemisphere during performance of a unimanual motor task.

Materials and methods

Subjects

Eighteen right-handed subjects meeting DSM-IV criteria for bipolar disorder (nine males and nine females) and 13 right-handed healthy subjects (seven males and six females) completed the study. Subjects were recruited from the community using web-based notices of research opportunities or brochures placed in community outpatient clinics. Subjects were included if they met DSM–IV criteria for bipolar disorder and passed screening for participating in procedures involving high magnetic fields. We applied strict neurologic exclusion criteria as most subjects we recruit for research participate in a larger program of research. Subjects with positive histories of neurologic illness, head trauma leading to loss of consciousness or history of electroconvulsive therapy (ECT) were excluded. Subjects were excluded if they met DSM-IV criteria for substance abuse or substance dependence disorder. The mean age of the BPD subjects was 44.9 ($\pm$11.2) years and the mean age for the healthy comparison subjects (36.5 $\pm$ 15.1 years). Groups were not significantly different in age. Eleven BPD subjects were taking mood stabilizers [divalproex (n = 6), lithium (2), carbamazapine (1), gabapentin (1), or topiramate (1)], 11 were on antidepressants [bupropion (5), fluoxetine (3), sertraline (2), or venlafaxine (1)] and seven were taking at least one antipsychotic medication [olanzapine (4), quetiapine (3), risperidone (1), or clozapine (1)] at the time of the scan. One patient was completely unmedicated at the time of the scan. An additional 12 subjects (three BPD and six normal comparison subjects) were enrolled but were excluded for various reasons, including excessive motion during the MRI procedures (six subjects) and scanner artifact (two subjects), and the presence of abnormally large ventricles for which an organic etiology was suspected (one comparison subject). All subjects signed institutional approved informed consent prior to undergoing study procedures. Data from the subjects of this study were part of a larger study involving fMRI of the basal ganglia and effects of medication and affective states (34). None of the present findings on the motor cortex appeared in the prior publication.

Clinical assessments

All subjects underwent a structured clinical interview (SCID) to ensure they met DSM-IV criteria for bipolar disorder. SCID interviews were conducted by a senior psychiatric nurse who had been involved in psychiatric research for over 10 years. This individual, along with other staff participating in diagnostic interviewers undergo periodic training to ensure high inter-rater reliability on the SCID and other clinical rating instruments. The results from the SCID diagnoses for bipolar subtypes revealed 11 subjects with mixed subtype, five with depressed subtype and two with manic subtype. In addition to the structured diagnostic interview, subjects were administered the 17-item Hamilton Depression Rating Scale (HDRS) (35) to rate severity of depression and the Young Mania Rating Scale (YMRS) (36) to rate severity of mania. The mean ($\pm$S.D.) HDRS score for the 18 bipolar subjects was 15.7 (10.72). The mean YMRS score was 4.7 (3.9). The time proximity between HDRS and YMRS ratings and scans ranged from 2 weeks to over 6 months. Ratings from the HDRS and YMRS that most closely approximated the scan data were used to classify subjects in depressed and manic subgroups. For the purpose of this study, subjects were classified as primarily

depressed if their HDRS total score was >7 and their YMRS total score was ≤3. Thus, depressed subjects exhibited symptoms of depression in the absence of significant mania. Subjects were classified as primarily manic (or hypomanic) if their YMRS score was >3 and they did not meet DSM-IV criteria for bipolar depression. Thus, manic subjects exhibited symptoms of mania and met DSM-IV criteria for manic or mixed subtype. On the basis of these criteria, there were six depressed and 12 manic bipolar subjects. The mean HDRS and YMRS total scores for the depressed subgroup were 22.3 (15.3) and 1.3 (1.7), respectively. The mean HDRS and YMRS total scores for the manic subgroup were 13.3 (5.8) and 6.4 (3.7), respectively. Manic patients had significantly higher YMRS scores than depressed patients ($t = 3.13$; $df = 16$; $p = 0.006$). The difference in HDRS total scores between depressed and manic patients did not reach statistical significance ($t = 2.04$; $df = 16$; $p = 0.059$). Five of the depressed patients met DSM-IV criteria for depressive subtype and one met criteria for mixed subtype. Ten of the manic patients met criteria for mixed subtype and two met criteria for manic subtype. The mean age of the six depressed subjects was 44.8 (±11.2) years. The mean age of the 12 manic subjects was 44.9 (±11.6) years.

Instrumentation

Thumb flexion movements were transduced using a pneumatic pressure transducer (Honeywell model 144PC01D7) connected to a hand-held rubber bulb. Thumb flexion, applied against the bulb, displaced air captured in a polyurethane tube. This imparted a change in the electrical current passing through a balanced Wheatstone bridge circuit and produced a proportional voltage change. The change in voltage was continuously displayed as a cursor on a computer monitor for the subject to see. An adjustable mirror was placed on the head coil for subjects to view simultaneously the stimuli and the cursor representing their applied pressure.

Reaction time task design

Two RT tasks were used in the present study to examine the effects of task complexity on regional brain activity and hemispheric asymmetry. The first was a SRT task involving rapid thumb flexion in response to a visual stimulus displayed on a computer screen. Subjects begin at rest until they see the word 'GO' appear on the screen, which served as a visual prompt to flex the thumb once as rapidly as possible and then to relax. SRT trials elicited rapid thumb flexion movements. SRT thumb movements were not visually guided. The second involved RT thumb movements to one of two targets. Thus, the second task was considered a CRT. Subjects were instructed to flex the thumb as quickly and accurately as possible to reach a target box displayed on the screen. There were two targets located at 15 and 30 degrees of thumb flexion. Four randomly presented targets were displayed over a 16-s interval. CRT trials were initiated by the appearance of the target box. Subjects were instructed to reach the target each time a box appeared on the screen and then to relax. Targets remained on the screen for 2 s to allow the subject sufficient time to see and move to the target. Contrasting intervals of rest were imbedded throughout the SRT and CRT trials during which the subject was instructed to relax the hand and not apply pressure to the bulb. Subjects were cued to these rest intervals with the phrase 'REST' appearing on the screen.

The SRT, CRT, and rest trials were delivered in 16-s blocks over a period of 288 s (4 min 48 s). Each RT block contained four trials. Thus, a single 288-s run consisted of 24 SRT trials (six blocks), 28 CRT trials (seven blocks), and five 16-s rest blocks. Blocks were randomized throughout the run. Two runs were administered for right hand trials and two for left hand trials in counterbalanced order across subjects. Fig. 1 shows a continuous movement waveform for a series of SRT, CRT, and rest blocks from one subject. Reaction times, in milliseconds, were calculated for the CRT and SRT trials.

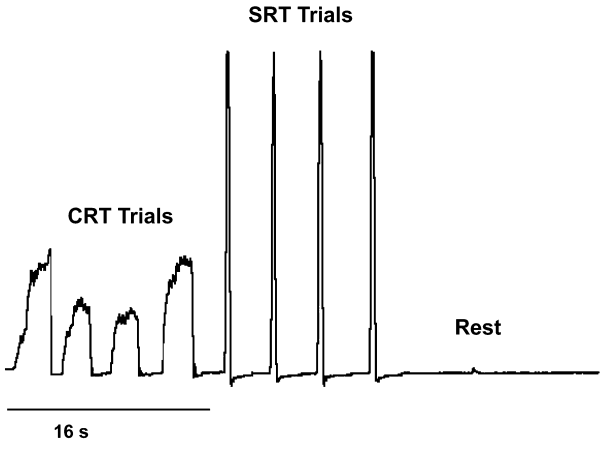

Fig. 1. Pressure waveform from behavioral task. Exemplary waveform showing subject's thumb flexion movements for 16-s choice reaction time (CRT), simple reaction time (SRT) and rest blocks. Figure shows four CRT movements to targets (not shown) and four SRT movements without targets. Presentation order is randomized.

fMRI acquisition. A 1.5 Tesla General Electric Signa scanner was used to acquire whole brain images. Spiral pulse sequences were employed because of their reduced sensitivity to subject motion. A high-resolution structural image of the entire brain was obtained using sagittally acquired 3D spiral Fast Spin Echo T_1 images (TR = 2000 ms, TE = 20 ms, TI = 700 ms, FOV = 240 mm, echo spacing = 15.6 ms, eight echoes, resolution = $0.9375 \times 0.9375 \times 1.328$ mm, 128 contiguous slices, 8 min 36 s). Functional scans were acquired using spiral imaging in the axial plane (TR = 4000 ms, TE = 40 ms, flip angle = 90°, FOV = 240 mm, 19–21 7-mm contiguous slices, 72 repetitions, 4 min 48 s) with a reconstructed in-plane resolution of 1.875×1.875 mm. The gradient echo recall pulse sequence weights the image for T_2* blood oxygen level dependent (BOLD) contrasts (37, 38).

Image processing. We used Analysis of Functional NeuroImages (AFNI) software (39) to analyze and visualize the image data. To further reduce the effects of motion from the functional time series data set, the echoplanar images were co-registered to the central image in the time series using a six-parameter (roll, pitch, yaw, anterior to posterior, superior to inferior, and lateral axes) 3D motion correction algorithm (39). Inspection of our image processing logs indicated that six normal comparison subjects and three BPD subjects were excluded because of excessive motion that could not be corrected using the 3D motion correction algorithm. The absolute mean displacements across all trials and for both hands for the 13 healthy comparison subjects were 0.03, 0.05, 0.02, 0.04, 0.02, and 0.01 mm for roll, pitch, yaw, anterior to posterior, superior to inferior, and lateral axes, respectively. The absolute mean displacements across all trials and for both hands for the 18 BPD subjects were 0.04, 0.05, 0.03, 0.04, 0.02, and 0.02 mm for roll, pitch, yaw, anterior to posterior, superior to inferior, and lateral axes, respectively. None of the group differences were statistically significant. The motion corrected BOLD signal intensities were then used as dependent variables in a multiple regression performed using AFNI's 3dDeconvolve program. The time-dependent signal was modeled with a combination of the following variables: reference vectors representing the occurrence of different behavioral blocks (i.e. rest, SRT, CRT), a linear trend, and a constant. A shift parameter (of two TRs) was also introduced into the model to account for delay in the hemodynamic response. The magnitude of each fit coefficient for the general linear contrast in signal intensity (controlling for the other parameters in the model) between SRT and rest, CRT and rest, and SRT and CRT at each voxel within the ROIs was used as the dependent variable for group analyses.

The structural images were then transformed into 3-dimensional volumes. The functional images collected during the same session were resampled into isotropic voxels (4.0 mm^3) and manually co-registered with the anatomical images. The anatomical and functional bricks were then transformed into the standardized coordinate system of Talairach and Tournoux (40).

In order to focus on the areas directly involved in the task as well as minimizing the number of within- and between-group comparisons, two cortical regions of interest (ROI) were defined in each hemisphere: (i) the primary motor cortex corresponding to Brodmann area 4 (M1); and (ii) the SMA corresponding to Brodmann area 6 (SMA). We chose these two cortical areas because of their prominent role in preparation (41) and execution (30) of RT movements and in complex tasks engaging both motor and cognitive dimensions (42). Furthermore, these cortical areas have been the focus of previous research on hemispheric asymmetry of movement (28).

The coordinates for and the extent of the ROI regions were determined using published values for the SMA and hand area of M1 (43). Masks were used to isolate regions of interest from which the fit coefficients were obtained. The anatomic boundaries, in 3-D Talairach coordinate space were +44 to +60 mm (inferior to superior), +18 to +44 mm (posterior to anterior), and +18 to +44 mm (medial to lateral) for M1 and + 52 to +68 mm (inferior to superior), +4 to +36 mm (posterior to anterior), and +0 to +12 mm (medial to lateral) for SMA.

Statistical analysis. Fit coefficients representing the RT minus rest contrast were calculated for each subject from runs using the left and right hands for the SRT and CRT tasks averaged across two runs. Thus, for each subject there were four fit coefficients available for statistical analyses. As magnitudes of the fit coefficients were derived from the general linear contrast in signal intensity between RT and rest at each voxel, positive fit coefficients reflect RT BOLD responses that were greater than rest. In addition, a hemisphere difference coefficient was calculated by subtracting the right hemisphere fit coefficients from the left hemisphere coefficients. Positive hemispheric asymmetry scores for right hand trials and negative

asymmetry scores for left hand trials reflected a contralateral bias in activation.

Initial statistical analyses consisted of examining group differences in RTs on the two behavioral tasks controlling for hand and task complexity using an analysis of variance (ANOVA). The effects of medication type on BOLD response and behavioral performance were examined using *t*-tests. To test the hypothesis that manic and depressed BPD patients differ in terms of hemispheric asymmetry as measured by BOLD response during fMRI after controlling for important factors such as response hand and task complexity, we used a three-way analysis of variance (ANOVA) with repeated measures. Between-group factors in the ANOVA included diagnostic group with three levels (healthy, depressed, manic), response hand (left and right), and hemisphere (left and right). Task complexity served as the within-group repeated measure with two levels (SRT and CRT). Significant simple main effects and interactions were examined using one and two-way ANOVAs. For all statistical analyses, a p-value of ≤ 0.05 was needed for significance.

Results

Behavioral data

Table 1 shows the performance on the behavioral tasks for three subject groups. Results from a three-way repeated measures ANOVA (group × hand × task) indicated a significant main effect for group ($F = 13.5$ df = 2,54; $p < 0.0001$), a significant main effect for task ($F = 11.5$ df = 1,54; $p = 0.001$), and a significant group × task interaction ($F = 7.7$ df = 2,54; $p = 0.001$). Post-hoc analyses indicated that depressed BPD subjects had significantly longer reactions times than manic BPD subjects ($F = 8.34$; df = 2,30; $p < 0.01$) and healthy comparison subjects ($F = 26.2$; df = 1,34; $p < 0.0001$) and that manic BPD subjects had longer RTs than healthy comparison subjects ($F = 6.22$; df = 1,44; $p < 0.02$). Analysis of performance on the SRT showed longer RTs than the CRT for depressed BPD patients only ($F = 5.9$; df = 1,10; $p < 0.05$).

fMRI findings

Hemispheric asymmetries in BOLD response. Table 2 shows the results of the three-way repeated measures ANOVA for the M1 asymmetry scores. The main effects for group and task were non-significant. However, there was a significant hand effect suggesting that use of different hands led to different hemispheric asymmetry scores for M1. None of the interactions were significant. *Post hoc* analysis of the hand effect revealed differences between manic and depressed BPD subjects only ($F = 4.45$; df = 1,32; $p < 0.05$) with the manic BPD subjects exhibiting less hemispheric asymmetry than the depressed BPD subjects for the left hand. These results are portrayed in Fig. 2. As shown in the figure, healthy subjects did not exhibit opposite asymmetries for left and right hands for M1; whereas BPD subjects exhibited a strong left hemisphere bias for right hand trials, especially for the CRT trials.

Table 3 shows the results of the three-way repeated measures ANOVA for the SMA asymmetry scores. The main effect for hand was statistically significant as was the task × hand interaction. Other main effects and interactions were non-significant although there was a trend for the group × hand ($p = 0.068$) and group × hand-task ($p = 0.052$) interactions to reach statistical significance. *Post hoc* analysis of the hand effect revealed significant difference between healthy comparison subjects and depressed ($F = 55.86$; df = 1,34; $p < 0.00001$) and manic ($F = 66.36$; df = 1,46; $p < 0.00001$) subjects and between depressed and manic subjects ($F = 38.19$; df = 1,32; $p < 0.00001$).

Post hoc analyses of the task × hand interaction for SMA revealed significant effects of task on hemispheric asymmetry score when contrasting healthy comparison with manic BPD subjects ($F = 7.55$; df = 1,46; $p < 0.01$) and depressed with manic BPD subjects ($F = 6.83$; df = 1,32;

Table 1. Mean (S.D.) reaction times, in milliseconds, for the simple RT (SRT) and choice RT (CRT) tasks for healthy subjects (n = 13), depressed bipolar disorder subjects (n = 6) and manic bipolar disorder subjects (n = 12)

	Healthy subjects		Depressed BPD subjects		Manic BPD subjects	
	L Hand	R Hand	L Hand	R Hand	L Hand	R hand
SRT	700.1 (108.5)	638.5 (123.3)	1002.5 (345.2)	976.0 (264.4)	774.8 (147.2)	763.5 (123.9)
CRT	702.7 (85.0)	673.0 (120.1)	764.2 (41.5)	757.3 (61.2)	732.0 (109.8)	723.7 (104.9)

See text for results of difference tests.

Table 2. Results of the three-way repeated measures ANOVA for the primary motor cortex (M1) hemispheric asymmetry scores

Factor	df	*F*	p
Group	2,56	0.14	0.86
Hand	1,56	3.85	0.05
Task	1,56	0.07	0.95
Group × Hand	2,56	1.08	0.34
Group × Task	2,56	0.26	0.77
Hand × Task	1,56	1.08	0.30
Group × Hand × Task	2,56	0.37	0.69

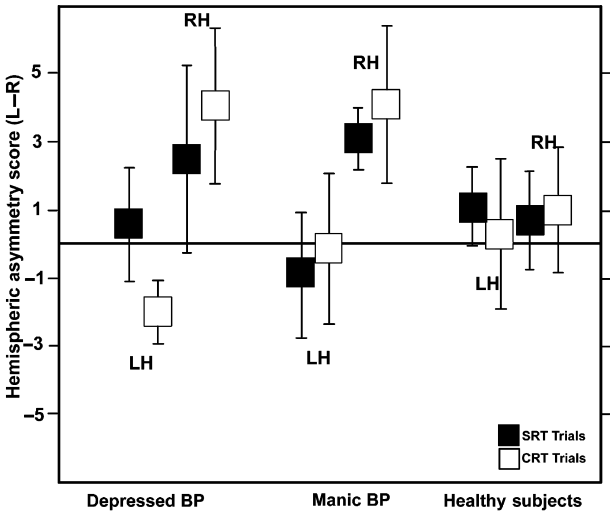

Fig. 2. Hemispheric asymmetry scores for the primary motor cortex (M1). Mean (S.E.M.) hemispheric asymmetry scores for three subject groups for left (L) and right (R) hand SRT and CRT trials for M1. Scores were derived by subtracting the fit coefficients for the right hemisphere from the left. Positive scores indicate greater left than right hemisphere fit coefficients; negative scores indicate greater right than left hemisphere fit coefficients.

Table 3. Results of the three-way repeated measures ANOVA for the supplementary motor area (SMA) hemispheric asymmetry scores

Factor	df	*F*	p
Group	2,56	0.06	0.93
Hand	1,56	76.18	<0.0001
Task	1,56	0.72	0.34
Group × Hand	2,56	2.82	0.06
Group × Task	2,56	0.49	0.61
Hand × Task	1,56	4.30	0.04
Group × Hand × Task	2,56	3.12	0.05

p = 0.01). Hemispheric asymmetry scores are plotted in Fig. 3. As shown in the figure, hemispheric asymmetry scores for SRT and CRT trials were similar for healthy comparison and depressed BPD subjects. For these groups, the asymmetry scores corresponded to greater activity in the hemisphere

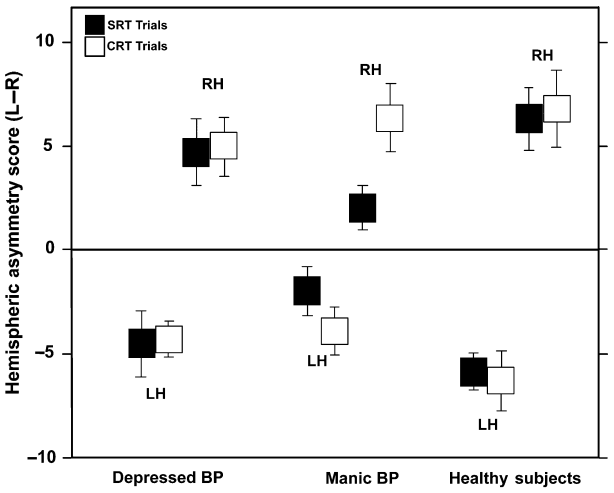

Fig. 3. Hemispheric asymmetry scores for the supplementary motor area (SMA). Mean (S.E.M.) hemispheric asymmetry scores for three subject groups for left (L) and right (R) hand SRT and CRT trials for the SMA. Scores were derived by subtracting the fit coefficients for the right hemisphere from the left. Positive scores indicate greater left than right hemisphere fit coefficients; negative scores indicate greater right than left hemisphere fit coefficients.

contralateral to the response hand used. However, the asymmetry scores for manic BPD subjects for the left hand trials (averaged across task condition) indicate less right hemispheric bias compared with depressed BPD or healthy comparison subjects.

Table 4 shows the mean (S.D.) fit coefficients for the normal healthy subjects, depressed, and manic BPD subjects for M1 and SMA. The table highlights M1 and SMA fit coefficients that are significantly different from zero (asterisks) and fit coefficients for the right hemisphere that are significantly different from the corresponding left hemisphere fit coefficients. Analyses of the hemispheric differences for M1 within subject group, within response hand, and within task revealed no left–right hemisphere differences for the healthy comparison or depressed BPD subjects; however, manic BPD subjects exhibited significant hemispheric difference for right hand SRT trials because of increased activity within the right hemisphere ($t = 3.45$; df = 11; p = 0.005). Analyses of the hemispheric differences for SMA within subject group, within response hand and within task revealed significant between hemisphere differences for healthy comparison subjects for all four contrasts. Depressed and manic BPD subjects failed to show significant between hemisphere differences for right hand SRT trials whereas only depressed BPD subjects failed to show significant between hemisphere differences for right hand CRT trials. The absence of hemispheric differences for depressed and manic BPD subjects could be

Table 4. Mean (S.D.) fit coefficients for the primary motor area (M1) and supplementary motor area (SMA) obtained during left and right hand simple RT (SRT) and choice RT (CRT) tasks in healthy subjects, depressed bipolar disorder subjects, and manic bipolar disorder subjects

		Healthy subjects		Depressed BPD		Manic BPD	
		Hemisphere					
ROI-Task	Hand	Left	Right	Left	Right	Left	Right
M1-SRT	L	1.91 (6.35)	0.81 (5.76)	2.29 (3.99)	1.76 (2.49)	3.64 (7.62)	4.55 (9.87)
	R	1.52 (5.49)	0.83 (4.00)	2.90 (6.23)	0.42 (1.91)	3.74 (4.92)*	0.63 (3.46)[a]
SMA-SRT	L	−1.71 (2.75)	4.17 (3.62)**[a]	−1.08 (2.97)	3.43 (3.30)[a]	0.19 (2.93)	2.19 (3.63)
	R	3.86 (5.06)*	−2.43 (2.09)[a]	4.82 (2.70)**	0.11 (2.63)	2.64 (1.94)***	0.61 (3.17)
M1-CRT	L	4.26 (7.62)	3.96 (6.38)*	0.69 (3.09)	2.68 (1.51)**	4.87 (6.72)	5.02 (10.73)
	R	1.40 (6.68)	0.42 (4.74)	5.20 (4.02)*	1.13 (3.13)	5.80 (8.13)*	1.69 (4.39)
SMA-CRT	L	−0.26 (3.48)	6.04 (4.39)***[a]	−0.26 (3.23)	4.05 (1.85)**[a]	0.64 (4.09)	4.55 (5.66)*[a]
	R	4.45 (6.28)*	−2.35 (2.17)[a]	5.19 (3.57)*	0.22 (3.89)	4.56 (3.31)***	−1.78 (4.15)[a]

Significantly different from zero at the level *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
[a]Right-left hemisphere differences within brain area and within task significant after Bonferroni correction.

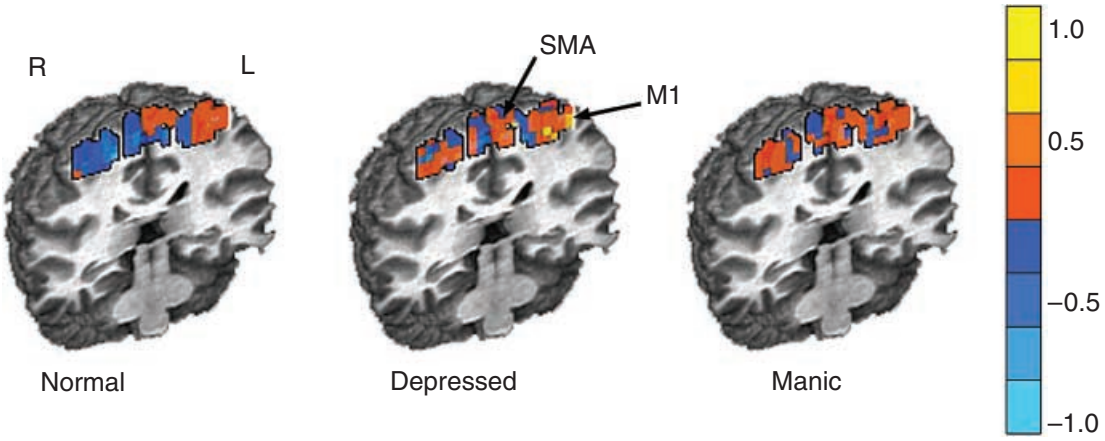

Fig. 4. Three-dimensional visual maps of effect sizes in motor cortex. Functional brain maps representing the effect sizes for the SRT-rest contrast for the three subject groups for right hand trials. The maps emphasize the group differences in BOLD responses in the primary motor cortex (M1) and the supplementary motor area (SMA). Hot colors (yellow and orange) indicate greater BOLD response for SRT than rest; cold colors (blue) indicate greater BOLD response during rest than SRT trials. Calibration bar shows effect sizes (Eta^2).

attributed to failures to inhibit right hemisphere activity.

Figure 4 shows functional brain maps representing the effect sizes for the SRT-rest contrast for the three subject groups for right hand trials. Note that the effect sizes in these maps were reduced relative to the group effect sizes because of lack of uniform activation within the ROI. That is, subjects did not always activate identical voxels within the ROI leading to increased variability and lowered effect sizes. However, these maps portray group differences in degree of asymmetry in both M1 and SMA.

Effects of medication type on behavioral response, BOLD response and hemispheric asymmetry. Table 5 lists the observed effects of medication type on behavioral responses, BOLD responses, and hemispheric asymmetry scores. Results are separated for antipsychotics, mood stabilizers, and antidepressants. Reaction times were affected only by mood stabilizers. Subjects taking mood stabilizers had significantly longer RTs than those off mood stabilizers. For the BOLD responses during the SRT task, subjects off antipsychotics or off mood stabilizers had significantly greater fit coefficients for the right SMA, and right and left M1 compared with subjects taking either of these medications. Regarding the hemispheric asymmetry scores, subjects taking antipsychotics had significantly less contralateral activation in the SMA than subjects off antipsychotics. Similarly, subjects taking antidepressants had significantly less contralateral activation in the M1 than subjects

Table 5. List of response variables on which bipolar disorder subjects treated with one of three medication types differed significantly from bipolar subjects off the medication. Shown are the mean (S.D.) reaction times (RT), BOLD response fit coefficients, and hemispheric asymmetry scores. Positive asymmetry scores indicate greater BOLD response for the left hemisphere; negative asymmetry scores indicate greater BOLD response for the right hemisphere

			Antipsychotics		Mood stabilizers		Antidepressants	
	Hand	Task	On	Off	On	Off	On	Off
Behavioral task								
RT (ms)	R	SRT			930.0 (114.1)[a]	707.8 (210.0)		
BOLD response								
R. SMA	L	SRT	0.52 (3.23)	3.93 (3.05)[b]				
L. M1	L	SRT			0.27 (4.49)	7.78 (6.87)[c]		
R. M1	L	SRT			0.50 (92.56)	8.52 (11.51)[d]		
Hemisphere asymmetry score								
SMA	L	SRT	−0.54 (3.66)	−4.31 (3.71)[e]				
M1	L	CRT					1.99 (4.09)	−5.09 (7.04)[f]

[a]Longer RT for subjects on versus off mood stabilizers; $t = 2.53$; df = 15; $p = 0.02$.
[b]Lower BOLD response for subjects on antipsychotics; $t = 2.26$; df = 16; $p < 0.05$.
[c]Lower BOLD response for subjects on mood stabilizers; $t = 2.81$; df = 16; $p = 0.01$.
[d]Lower BOLD response for subjects on mood stabilizers; $t = 2.26$; df = 16; $p < 0.05$.
[e]Less lateralized response for subjects on antipsychotics; $t = 2.11$; df = 16; $p < 0.05$.
[f]Subjects on antidepressants had opposite hemispheric asymmetry than subjects off antidepressants; $t = 2.71$; df = 16; $p = 0.01$.

off antidepressants. Thus, antipsychotics and mood stabilizers appeared to reduce the magnitude of the BOLD response in the motor cortex. Antipsychotics and antidepressants appeared to reduce the contralateral hemispheric bias normally present in M1 and SMA during a unimanual RT task.

Discussion

The present study had three general findings. First, the thumb flexion RT tasks employed in this study elicited strongly lateralized activity in the SMA in healthy individuals. Activity in primary motor cortex was also evident during the motor task; however, unlike SMA, M1 activity was biased in favor of the left hemisphere for both hands in healthy subjects. Secondly, during performance of the thumb flexion RT tasks, normal healthy subjects activated the SMA in a reciprocal fashion with significantly greater activity in the left SMA for right hand trials and the right SMA for left hand trials. Depressed BPD subjects failed to show this normal reciprocity for right hand trials indicating a failure to suppress unwanted activity in the ipsilateral right SMA. Manic BPD subjects exhibited the normal reciprocal activation pattern in the SMA for CRT trials but not SRT trials during which these subjects failed to suppress unwanted ipsilateral activity in both hemispheres. There was a general finding for manic and depressed BPD subjects to exhibit greater activity in the left primary motor area especially for the right-handed CRT trials suggesting increased cortical excitability. Thirdly, BPD subjects taking antipsychotic or mood stabilizing medications at the time of the scan exhibited longer RTs, lower BOLD responses in M1 and SMA, and a loss of normal hemispheric asymmetry in the SMA. Subjects taking antidepressants at the time of the scan exhibited opposite hemispheric asymmetries in M1 compared with subjects off antidepressants.

One general observation of the present study was the predominance of SMA activation relative to M1 for RT thumb movements during the SRT task. Normal healthy and depressed BPD subjects were less likely to exhibit activity in the primary motor cortex than manic BPD subjects. It is possible that over the course of the run, normal healthy subjects developed a strategy whereby the SMA took over the primary role of initiating simple unguided movements from the primary motor cortex, whereas manic BPD subjects may not have reallocated control of movement initiation, at least in the left hemisphere. The lack of consistent M1 activity for healthy and depressed BPD subjects may reflect the ability of these subjects to transfer control from lower to higher cortical centers. Studies of normal hemispheric control of movement have demonstrated that the SMA is involved in the initial programming phase of movement (44), functioning as a higher programming center for motor control (45).

Group differences were observed on the hemispheric asymmetry scores. The most striking difference was found for the SMA. Normal healthy subjects exhibited contralateral activation and ipsilateral suppression in the SMA leading to significant hemispheric difference scores. While

depressed and manic BPD subjects exhibited this response pattern for most of the left hand trials, the right hand trials lacked this asymmetric pattern. Inspection of the fit coefficients revealed that BPD subjects failed to suppress or inhibit right hemisphere activity during right-handed trials (see Table 4). This apparent disturbance extended to the left hemisphere as well in manic BPD subjects. Thus, our primary hypothesis that manic BPD subjects would exhibit an increase in right hemisphere activity was supported by the SMA asymmetry scores.

The second pattern of abnormality we observed was an increase in hemispheric asymmetry in M1 among manic BPD subjects. Only manic subjects exhibited an M1 asymmetry. Inspection of the fit coefficients indicated that this asymmetry was because of an increase in left hemisphere activity during right-handed trials (see Table 4). Thus, our secondary hypothesis that manic and depressed BPD subjects would exhibit opposite hemispheric asymmetries was partially upheld by the M1 asymmetry scores.

The only published PET study reporting abnormalities in the motor cortices of BPD subjects during performance of a motor task found increased rCBF in the right SMA (19). We also found increased activity in the right compared with left SMA (in both depressed and manic subjects). However, it is difficult to conclude that these two studies had compatible findings. First, the previous PET study utilized a bimanual rather than a unimanual RT task. Thus, while our findings demonstrate a breakdown in the contralateral organization of the motor cortices, it is difficult to interpret the PET study because of the bimanual nature of their task. Secondly, we studied predominantly depressed and manic BPD subjects, whereas euthymic subjects were enrolled in the PET study. It may be that the right hemisphere hyperactivity during motor performance is not state dependent. The findings of the present study are consistent with our previous laboratory studies of motor function in bipolar mania (26, 27). In those studies, we found greater abnormality during left hand motor performance than right hand in BPD subject suggesting right hemisphere dysregulation. The present fMRI finding of right SMA hyperactivity in depressed or manic BPD disorder could explain the abnormal performance on the force steadiness measure we observed in prior studies. One of the roles of the SMA is to integrate sensory feedback from the basal ganglia and thalamus into the motor plan and to forward an updated motor plan to the primary motor cortex (44–46). Examining the contralateral SMA activity for SRT versus CRT tasks from Table 4 shows greater activity during the CRT trials for all subject groups suggesting a more active role for the SMA for tasks utilizing peripheral feedback. Thus, the contralateral SMA appears to function normally in BPD disorder; however, the present findings suggest that BPD subjects have difficulty inhibiting unwanted sensorimotor information processing taking place in the right hemisphere.

The use of antipsychotics, mood stabilizers, and antidepressants significantly reduced both the behavioral and BOLD responses associated with the RT tasks in our BPD subjects. There have been very few functional neuroimaging studies of the effects of pharmacotherapy on regional brain activity in psychosis patients and those that have been published either involved subjects with schizophrenia and not BPD (47, 48) or reported medication effects on subcortical brain regions rather than cortical areas (34). While not entirely compatible with the present study, these studies permit the generalization of the present findings to the broader effects of antipsychotic medications on brain activity. Braus et al. (47) compared blood flow changes in the primary motor cortex and SMA in groups of neuroleptic-naive first-episode and medicated schizophrenia patients. They found significant reduction in BOLD response in the motor cortices in patients treated with antipsychotics compared with those treated with unmedicated patients or healthy controls. Subjects on conventional antipsychotics exhibited less activation than those on atypical antipsychotics. The authors interpreted this latter finding as a demonstration of major differences between atypical and conventional antipsychotics. Muller et al. (48) reported significant increase in BOLD response in the motor cortex in unmedicated schizophrenia patients compared with medicated patients, while patients treated with either haloperidol or olanzapine exhibited under-activation compared with healthy controls. These results indicate that psychosis may manifest as over-activation in motor cortical areas and that antipsychotic medications reduce this over-activation to levels lower than that observed in healthy individuals. In our previous study of medication effects on subcortical brain areas during performance of a motor task in BPD subjects, we found significantly reduced BOLD responses in the globus pallidus, putamen, and thalamus in subjects treated with antipsychotic medications. Thus, the present findings together with the previous literature suggest that even atypical antipsychotic medications can diminish activity in both cortical and subcortical motor areas and that these effects are not specific to one

form of psychotic illness over another. The mechanism by which atypical antipsychotics lower cortical response is not clear. However, PET studies have shown that while all effective antipsychotics have significant dopamine D_2 receptor occupancy (49) conventional antipsychotic medications increase blood flow to the striatum (50), whereas atypical antipsychotics appear to decrease striatal metabolism (51). Studies of cortical metabolic effects related to antipsychotic medications (52, 53) show similar reductions in medial and lateral frontal cortex. From what is known about the motor circuitry and the striatopallidal inhibitory and excitatory projections (32, 33), alterations of striatal metabolism can lead to reduced thalamocortical excitation. Specifically, a decrease in metabolic activity involving excitatory striatal dopamine D_1 receptors could lead to an increase in GABAergic inhibition of thalamocortical projections via the direct circuit; whereas an increase in metabolic activity involving inhibitory striatal dopamine D_2 receptors could lead to an increase in GABAergic inhibition of thalamocortical projections via the indirect circuit. Thus, the cortical changes reported in this and previous studies may be secondary effects of antipsychotic actions on striatopallidal function. The hypothesis that diminished cortical activity associated with antipsychotic medications may be secondary effect is borne out by the observation that these effects were found for the SMA and not M1. According to the circuit models, thalamocortical projections target higher level motor cortical areas such as the SMA. However, at least one PET study found that both conventional and atypical antipsychotic medications targeted cortical D_2 dopamine receptors (54).

Antipsychotics were not the only type of medication found to reduce cortical activity during a motor task in BPD subjects. We also found that subjects taking mood stabilizers exhibited lower BOLD responses particularly in the primary motor area and longer RTs than subject off mood stabilizers. It is well known that anticonvulsants inhibit excessive neuronal activity, albeit by several mechanisms (55). On the basis of the results of this study, such reduction in neuronal activity manifested as an increase in RT and reduced BOLD response in the primary motor areas, bilaterally. Three mechanisms have been proposed for this effect including blockade of voltage-gated sodium channels; enhancement of inhibitory GABAergic neurotransmission, or inhibition of excitatory glutamatergic neurotransmission (see ref 56 for review). Both GABAergic and glutamatergic mechanisms could explain the suppression of cortical activity via mechanisms described above for antipsychotics. Glutamate is the main excitatory neurotransmitter in the mammalian brain and the metabolic precursor of GABA (56). Pharmacotherapies that modulate these neurotransmitters are likely to have a direct impact on cortical excitability. Indirect mechanisms underlying reduced cortical excitability are also possible. For example, in a PET study of [^{18}F]DOPA, Yatham and colleagues (57) observed significant reduction in striatal dopamine neurotransmission following treatment with divalproex in manic BPD subjects. Their findings suggest a pre-synaptic mechanism as the site of action for divalproex. Confirmation of the present findings of motor cortical suppression in patients treated with mood stabilizers would support the idea that functional neuroimaging may be useful as a positive predictor of treatment efficacy in BPD.

One novel finding of the present study was subjects on psychotropic medications at the time of the scan had a reduced hemispheric asymmetry score for SMA and a reversal of the hemispheric asymmetry score for M1 compared with subjects off psychotropic medications. The altered hemispheric asymmetry scores for M1 in subjects on antidepressants and SMA in subjects on antipsychotics could be related to the same changes: either an increase in activity in the left hemisphere or a decrease in the right hemisphere, or both. Since the effect of antipsychotics was to reduce activity in the right SMA, it is likely that the antipsychotic-induced reduction in normal asymmetry may be related to a decrease in activity in the right hemisphere. There is insufficient data to speculate on how antidepressants could impart a reversal of the normal asymmetry in M1.

We are aware of several limitations of the present study. While the anatomic boundaries separating the SMA and M1 can be clearly identified using published guidelines (e.g. ref 44), the method poses two potential problems. First, subtle inter-hemispheric differences in the boundary can be lost during the Talairach normalization procedures. Secondly, normalization errors can be extended into the ROI analysis. We made no attempt to quantify or control for these errors; however, the same normalization approach was applied to all subjects and it is not likely that the results of this study could be affected by systematic error affecting one group of subjects more than another. Also, the published landmark coordinates we used for the present study were derived from a large series of normal brains (43) for identifying M1 and SMA and contained differed for left and right hemispheres. Therefore, we are confident that the group differences in hemispheric asymmetry we

observed in the present study were not influenced by systematic errors related to normalization. Despite potential problems associated with anatomic normalization that are unique to studies of brain asymmetry and in the absence of literature to suggest the contrary, we believe that the within-individual variation within the M1 and SMA boundaries was markedly lower than the between-subject variation. It is also possible that the ROIs may have included active voxels unrelated to the task. We made no attempt to remove the effects of non-associated voxels from within the ROIs. We reasoned that non-associated active voxels reflected noise inherent in the system and that this noise should be randomly distributed and would therefore not impose a systematic effect.

Aspects of the study related to performance during the RT task pose additional limitations. Because the healthy comparison and BPD subjects differed in terms of their performance on the RT tasks, we do not know that the group differences in cortical BOLD response during the RT tasks were a reflection of hemispheric dysfunction that existed as part of the bipolar illness or if the differences were the result of performance differences observed during the study. Had the two groups performed similarly, we would speculate that the abnormal cortical BOLD responses were either trait characteristics or some forms of compensation. However, we did not observe performance differences between manic and depressed subjects, yet there were a number of differences in BOLD response patterns as well as hemispheric asymmetry scores between these two groups of subjects. Also, as we only measured one hand per experiment, we were unable to monitor the non-test hand to ensure that it was not actively moving in response to the RT stimuli. Therefore, it is possible that some subjects were flexing both hands during the task, which would lead to aberrant hemispheric laterality. If the manic subjects were more inclined to do this (given our observation of increased cortical excitability in M1 for this group) than depressed or healthy comparison subjects, our group differences may have been more associated with following task directions rather than motor cortex physiology.

Limitations in the procedures used to classify depressed and manic BPD subjects warrant further discussion. The majority of our subjects met DSM-IV criteria for mixed state bipolar disorder. Thus, classification based solely on DSM-IV criteria was not possible. Instead, we classified subjects into depressed or manic groups according to a combination of DSM-IV criteria and symptoms. It is possible that our results may have differed if we applied strict DSM-IV criteria for classifying subjects. A second limitation pertains to delays between the time we obtained data on the nature and severity of symptoms and the time subjects underwent fMRI. For some subjects this time delay was on the order of months. Given the cyclic nature of bipolar disorder, it is possible that the symptom profiles of these subjects had changed over this time interval. Thus, the present findings showing differences in brain function across mood states must be considered preliminary. Differences in brain function between healthy subjects and BPD subjects (regardless of affective state) and the effects of medication on brain function in BPD were not influenced by this methodologic limitation.

In summary, the results of the present study demonstrate the presence of altered function in motor cortical activity during the production of simple thumb movements in BPD, particularly in the right SMA. The dysfunction was characterized by excessive activity during ipsilateral hand movements. A similar disturbance was found for the left hemisphere in manic BPD. Medications commonly used to manage the symptoms of BPD were found to suppress activity throughout the motor cortices with greater effects in the primary motor area, bilaterally. The presence of a right hemisphere disturbance in BPD is consistent with the hypothesis that the right hemisphere may be dominant in mood regulation. The presence of both left and right hemisphere disturbances in mania may explain the coexisting psychotic and affective symptoms observed in this condition. The use of a motor task as a proxy for localizing cortical and subcortical dysregulation of mood requires further study. The optimal study design would consist of scanning BPD subjects repeatedly under different mood states. Such longitudinal studies are currently underway in our laboratory.

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