

Research report

Striatopallidal regulation of affect in bipolar disorder

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Received 21 April 2005; received in revised form 8 January 2006; accepted 16 January 2006

Available online 24 February 2006

Abstract

Background: Evidence from the neuroimaging literature suggests that the basal ganglia plays an important role in the regulation of affect. This conclusion stems almost exclusively from group comparisons and it remains unclear whether previous findings can be confirmed from a longitudinal study of mood change. The aim of this study was to increase our understanding of the functional role of the basal ganglia and thalamus in relation to change in affect in patients with bipolar disorder.

Methods: Ten bipolar disorder subjects participated in a functional MRI study. We used a simple motor reaction time task to probe subcortical regions bilaterally. Subjects were scanned twice, once when their self-reported mood ratings indicated hypomania or euthymia and then again when they were in depressed states.

Results: Subjects in their euthymic or hypomanic states exhibited increased caudate activity bilaterally and the globus pallidus of the left hemisphere. Longitudinal analyses revealed a significant association between an increase in severity of depression and a decrease in activity in the external segment of the right globus pallidus.

Conclusions: Our findings suggest that the globus pallidus is less responsive during a simple motor task in the depressed compared to the normal or euthymic states in patients with bipolar disorder. These results are consistent with current physiologic models of basal ganglia circuitry in which an increase in caudate activity results in an increase in inhibitory GABAergic outflow to the external globus pallidus and subsequent decrease in thalamocortical excitation and may underlie the clinical manifestations of depression in bipolar disorder.

Limitations: The findings of this study need to be interpreted with caution as correlation coefficients may be overestimated in this small study sample.

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Keywords: Bipolar disorder; Functional MRI; Basal ganglia; Depression

1. Introduction

There are theoretical and clinical reasons to believe that the basal ganglia may be involved in bipolar disorder and depressive illnesses. Several neuroimaging studies confirm an important role of subcortical brain regions in the pathogenesis of mood disorders (Soares and Mann,

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1997; Drevets et al., 1997; Blumberg et al., 2000; Strakowski et al., 2000; Brambilla et al., 2001; Bearden et al., 2001; Mayberg, 2001; Caligiuri et al., 2003; Strakowski et al., 2005). While these studies have advanced our understanding of the neurobiology of mood disorders, they leave several questions unanswered. For example, there is a bias toward structural neuroimaging because systematically varying mood state for functional imaging is problematic (with the work of Mayberg, 2001 being a notable exception). Also, there are no studies describing the functional neuroanatomic effects of changes in mood state within the same individual over extended periods of time. It would be particularly helpful to know whether the changes in subcortical brain activity parallel changes in affect in bipolar disorder patients with cycling mood states.

The basal ganglia and thalamus govern multiple aspects of human behavior including emotion, sensation, and motor function. Given the difficulty in controlling change in mood states within a single experimental session necessary to undertake a functional neuroimaging study, it seems reasonable to consider other behaviors that not only share neural circuitry with affective behavior, but that track mood state over time, and can be exploited in the neuroimaging setting. Motor function satisfies these criteria for a valid proxy measure in studies of affect. Diagnostically, motor phenomena are recognized by the DSM-IV as primary features of depressive disorders. Psychomotor disturbances in depressed states are observable manifestation reflecting an increase in activity or slowing of activity. Psychomotor retardation has been considered a major feature of depressive disorders (Widlöcher and Ghozlan, 1989; Parker et al., 1993) with rates of agitation and retardation in depressive disorders range from 46% to 67% (Buchwald and Rudick-Davis, 1993; Sobin and Sackeim (1997). Psychomotor characteristics have been found useful in distinguishing bipolar from unipolar depression (Akiskal, 2005). Recent evidence implicates psychomotor agitation as an independent and clinically significant factor predicting suicidal ideation in depression (Akiskal and Benazzi, 2005). From the anatomical perspective, both affect and motor functions are regulated by common basal ganglia-thalamocortical circuits (Alexander and Crutcher, 1990). Motor and limbic structures converge at several junctions within these circuits particularly the nucleus accumbens (Powell and Lehman, 1976; Graybiel and Ragsdale, 1983). This convergence at the level of the striatum among the functionally distinct basal ganglia circuits offers the strongest evidence for “motor-affective” integration.

Insofar as basal ganglia circuits constitute the neuroanatomic foundation for the functional integration

between motor and affective behavior, we reasoned that a neuroimaging study of motor function in fluctuating mood states could provide new insight into the role of the basal ganglia in mood regulation. The aim of this study was to increase our understanding of the functional role of the basal ganglia and thalamus in relation to change in affect in patients with bipolar disorder.

2. Methods

2.1. Subjects

Ten subjects (4 men and 6 women) participated in this study. All met DSM-IV criteria for bipolar disorder and signed institutional-approved informed consent prior to participating. All subjects participated in previously published cross-sectional fMRI study of mood and medication effects in bipolar disorder (Caligiuri et al., 2003); however the results from the follow-up scans have not been previously published. Subjects had a mean (SD) age of 49.5 (11.9) years and a mean education of 16.1 (2.6) years. Seven subjects met DSM-IV criteria for depressive subtype; two for manic subtype; and one for mixed subtype. Nine of the 10 subjects were treated with psychotropic medications at the time of the scans. Of these subjects, seven were on an antidepressant, six were on a mood stabilizer, and three were on an antipsychotic. Six of the nine subjects were treated with more than one type of medication.

Subjects met eligibility for longitudinal study if they reported the presence of symptom change within a 12-month period. Subjects were initially identified as depressed, euthymic, or hypomanic using a brief self-rated mood scale (see below) on their first visit and then rated a second time within a 12-month period. If the mood symptom changes appreciably, they were scheduled for a second fMRI scan. Subjects also had to be on stable pharmacotherapies over the study period. Thirteen subjects were initially enrolled into the study and underwent their first MRI brain scan; however three subjects were excluded from further study because of a change in medication. The mean interval between first and second scan was 11.6 (4.5) months.

2.2. Clinical measures of affect

Severity of mania and depressive mood were quantified using a visual analog scale referred to as the Simplified Mood Scale (SMS). We chose the SMS to rate mood over other formal ratings scales because the SMS required only a few minutes to complete and could be administered immediately before entering the MRI

scanner. The SMS uses a continuous 100mm linear scale. The scale consisted of seven items and was self-rated. Self-ratings were made for each of the seven items (mood, movement, energy, appetite, enjoyment, thinking, and speech) by marking a circle on a horizontal line labeled from zero (lowest) to 100 (highest). A total SMS score was calculated by adding the ratings for the seven items. Using this scale, ratings of 50 on any item represented optimal state. The SMS was validated using an independent group of 42 subjects with ($n=16$) or without ($n=26$) mood disorders. A discriminant function analysis was used to evaluate the sensitivity and specificity of the SMS total score and mood item. Results indicated 92% specificity and 75% sensitivity with an overall correct classification of 85.7%. We also obtained ratings from 35 healthy subjects to identify cut-point for classifying patients as depressed or manic. The normal mean (SD) was 69.3 (15.7) on the mood item and 495.5 (101.5) on the total scale. Thus, a self-rating of 50 on this scale does not necessarily reflect “normal” mood.

2.3. Image acquisition

2.3.1. Motor probe

We used a simple reaction time (SRT) task to probe basal subcortical activity. The SRT task involved rapid thumb flexion in response to a visual stimulus displayed on a computer screen. The apparatus used to record thumb flexion movements consisted of a pneumatic pressure transducer (Honeywell model 144PC01D7) connected to a hand-held rubber bulb. Flexion of the thumb at the proximal joint against the bulb displaces air captured in a polyurethane tube and imparts a change in the electrical current passing through a balanced Wheatstone bridge circuit and produces a proportional voltage change. The change in voltage was graphically displayed continuously as a cursor on a computer monitor for the subject to see. When at rest, the subject’s cursor was positioned on the right edge of the display (baseline). The visual cue appeared in the middle of the screen prompting the subject to flex their thumb. Flexing the thumb caused the subjects cursor to move from right to left and once relaxed, the cursor returned to baseline. An adjustable mirror was placed on the head coil for subjects to view the display. The visual cues and subject’s pressure responses were presented from the computer’s video output projected through a shielded window onto a screen positioned approximately 3m from the subject’s head.

Subjects responded to a visual stimulus by flexing their thumb as rapidly as possible. Trials began with the subjects at rest. There were four trials for each 16-s half block followed by a 16-s rest. The visual cues were

delivered every 2s and remained on the screen for 2s. There were four runs for each subject: two during which the left hand was used and two during which the right hand was used. Results from the two runs for each hand were averaged prior to statistical analyses and separate analyses were performed for the left- and right-hand trials.

2.3.2. Image acquisition

We used a 1.5 Tesla General Electric Signa scanner to acquire whole brain images. Spiral pulse sequences were employed because of insensitivity to subject motion. A high-resolution structural image of the entire brain was collected using sagittally acquired 3D spiral Fast Spin Echo high-resolution images (TR=2000ms, TE=20ms, TI=700ms, FOV=240mm, echo spacing=15.6ms, 8 echoes, resolution= $0.9375 \times 0.9375 \times 1.328$ mm, 128 contiguous slices, 8min 36s). Functional scans were acquired using spiral imaging in the axial plane (TR=4000ms, TE=40ms, flip angle=90°, FOV=240mm, 20 7-mm contiguous slices, 105 repetitions, 7min) with a reconstructed in-plane resolution of 1.875×1.875 mm. The gradient echo recall pulse sequence weighed the image for blood oxygen level dependent (BOLD) contrasts (Bardettini et al., 1995; Ogawa et al., 1990).

2.4. Image analysis

Analysis of Functional NeuroImages (AFNI) software (Cox, 1996) was used for image analysis. The image analysis consisted of the following steps for each run. Using the AFNI 3d Deconvolve Program (Ward, 1997) time course data in each pixel was correlated with an a priori reference vector. The reference vector modeled the 16s off/on cycle of the baseline and experimental condition by assigning zero to a baseline acquisition and one to an experimental acquisition. The reference function was time-shifted as a procedure to optimize fit to the cerebrovascular response. This was accomplished by time-shifting the square-wave steps in 2s steps up to 6s forward to produce a reference vector approximating the time course of the cerebrovascular response to alterations in neural activity (Brown et al., 1999). Fit coefficients for the best-fit, shifted trapezoidal reference function were used as measures of functional contrast in all subsequent analyses. Thus, the fit coefficients were proportional to the difference in means for the SRT conditions minus resting condition and reflect the functional contrast between these conditions and served as the dependent variable. We use the term “BOLD response” to refer to the magnitude of the fit coefficient throughout the paper.

The structural images were transformed into 3-dimensional volumes. The functional images collected during the same session were resampled into isotropic voxels (4.0mm^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 (1988).

To minimize the number of within- and between-group comparisons we performed a region of interest (ROI) analysis. There were five ROIs including the putamen, the head of the caudate, the internal and external segments of the globus pallidus (GP), and the thalamus. ROIs were delineated using criteria and landmarks described in a previous study (Caligiuri et al., 2003). Analyses were performed for both left- and right-hemispheres. Statistical analyses consisted of converting the mood ratings and fit coefficients to change scores by subtracting the scores associated with the lower or depressed mood state (referred to as scan 2) from scores associated with the euthymic or elevated mood state (referred to as scan 1). Positive change scores always reflected higher ratings or fit coefficient for scan 1 compared to scan 2.

3. Results

3.1. Symptom ratings

Table 1 shows the SMS mood item ratings for scan 1 and scan 2 for the 10 study subjects. The mean (SD) self-

Table 1
Demographics and results of self-reported mood state prior to the two fMRI scans for the 10 bipolar disorder subjects of the study

Gender	Age	Subtype ^a	SMS scan 1	SMS scan 2	Psychotropic medications
M	49	Depressed	65 ^b	35 ^c	Lithium, loxapine, olanzapine
F	28	Depressed	87	43	Depakote, fluoxetine, bupropion
M	49	Manic	74	51	Depakote, fluphenazine, topiramate, olanzapine, quetiapine
F	65	Mixed	74	66	Depakote, venlafaxine
M	60	Depressed	80	54	Fluphenazine, bupropion
F	45	Depressed	76	43	Depakote, quetiapine
M	50	Depressed	65	55	Fluphenazine
F	61	Depressed	65	29	Fluphenazine, bupropion
F	55	Depressed	59	22	Depakote, gabapentin, sertraline, bupropion
F	33	Manic	71	31	None

Medications were unchanged between scan 1 and scan 2.

^a Based on DSM-IV criteria during first assessment.

Table 2

Mean (SD) BOLD responses for each ROI for left- and right-hand trials

Subcortical ROI	Left-hand trials		Right-hand trials	
	Scan 1	Scan 2	Scan 1	Scan 2
<i>Left hemisphere</i>				
GP internal	-5.09 (9.53)	-2.19 (10.98)	1.37 (5.61)	-1.05 (5.96)
GP external	-0.37 (3.86)	-2.93 (9.55)	1.38 (3.52)	-0.63 (4.23)
Thalamus	0.55 (3.02)	-2.59 (5.21)	0.62 (4.85)	0.49 (4.78)
Caudate	0.26 (3.58)	1.19 (5.20)	0.44 (8.33)	-1.54 (4.89)
Putamen	-0.34 (4.45)	-1.51 (6.94)	0.45 (2.66)	0.37 (2.15)
<i>Right hemisphere</i>				
GP internal	-2.66 (11.23)	2.42 (8.18)	-3.06 (6.62)	1.05 (6.09)
GP external	-2.18 (4.71)	2.39 (3.74)*	0.31 (4.37)	0.52 (4.65)
Thalamus	0.36 (4.45)	-1.52 (4.18)	1.23 (3.99)	-0.37 (3.88)
Caudate	-1.82 (6.89)	-4.18 (8.30)	-1.71 (5.11)	-2.01 (4.34)
Putamen	-1.23 (6.42)	-1.07 (4.72)	-0.04 (3.25)	0.20 (3.39)

* Significantly greater than scan 1 ($t=3.60$; $df=9$; $p<0.01$).

rated mood score obtained when subjects were scanned while mood was elevated was 71.6 (8.3). Based on an unpublished normative sample, four of the 10 subjects reported elevated mood during scan 1, with scores exceeding the upper 95% confidence interval of the normal mean (75). Subject self-reports for the SMS mood item decreased significantly ($t=7.49$; $df=9$; $p<0.0001$) during scan 2 to 42.9 (13.7). Based on our normative sample, nine of the 10 subjects reported depressed mood, with scores below the lower 95% confidence interval of the normal mean (64.0). The total SMS score for scan 1 was 432.9 (73.4) and 353.4 (117.8) for scan 2. These two scores were not significantly different.

3.2. Correlation between SMS ratings and fMRI BOLD responses

Table 2 shows BOLD responses for each ROI for scan 1 and scan 2. Correlational analyses revealed several associations between total and mood item ratings of the SMS and BOLD responses in the basal ganglia for scan 1 (elevated mood state) only. For right-hand trials, we observed significant relationships between the total SMS score and the left ($r=0.84$; $p=0.002$) and right ($r=0.75$; $p=0.013$) caudate nucleus. There was a significant

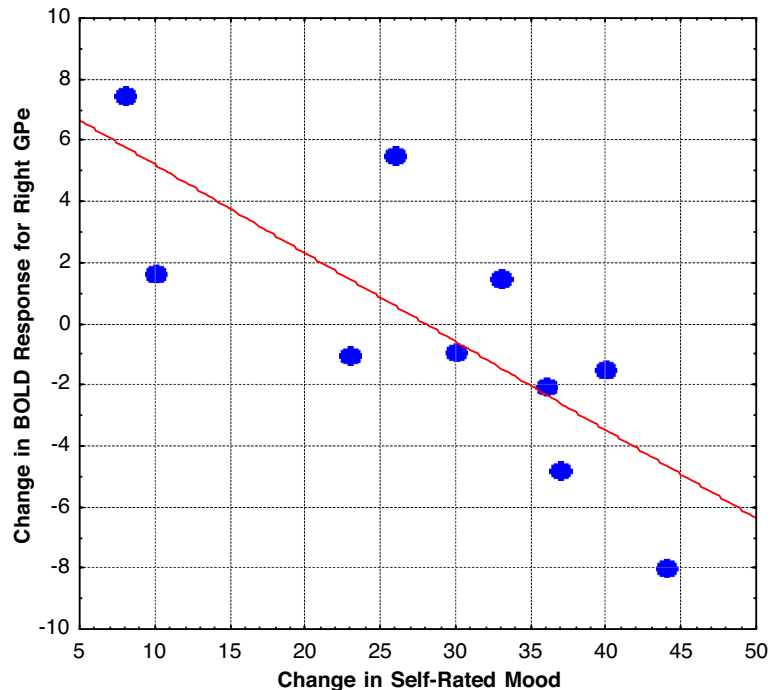


Fig. 1. Scatterplot showing the relationship between change in BOLD response for the right external segment of the globus pallidus and change in self-rated mood. See text for calculation of change scores.

correlation between the rating on the mood item of the SMS and the left external segment of the globus pallidus ($r=0.84$; $p=0.002$). These positive correlations indicate that increased scores on the total SMS score (reflective of increased mood, appetite, activity, enjoyment, thinking, and expressive speech) were associated with increased activity in the head of the caudate nucleus bilaterally and the left globus pallidus.

3.3. Change in affect and change in BOLD response

We performed a series of correlational analyses to examine the relationships between change in affective state and change in subcortical BOLD responses. Change scores were calculated by subtracting the SMS rating obtained during scan 2 (the visit with the lower self-rating, see Table 1) from those obtained during scan 1 (the visit with the higher self-rating). Change in BOLD response was calculated by subtracting the fit coefficients of scan 2 from the fit coefficients of scan 1. Positive difference scores for the SMS indicate larger reductions in mood state and positive BOLD difference scores indicate larger reductions in BOLD responses over the study period.

Analyses revealed significant associations between BOLD change score for the right external segment of the GPe and change in the SMS mood item ($r=-0.77$; $df=9$;

$p<0.01$). This negative relationship indicates that increases in depression severity were associated with decreases in activity in the right external segment of the globus pallidus over the course of the study. This finding is consistent with the significant increase in BOLD response for the right external segment of the globus pallidus ($t=3.60$; $df=9$, $p<0.01$) from scan 1 (higher SMS self-ratings reflecting euthymic or hypomanic state) to scan 2 (lower SMS self-ratings reflecting depressed state) for left-hand trials (see Table 2). This relationship is depicted in Fig. 1. We also found a significant association between BOLD change score for the right caudate nucleus and change in total SMS score ($r=0.76$; $df=9$; $p=0.01$). This positive relationship indicates that increase in overall depression severity was associated with an increase in activity in the right caudate nucleus.

3.4. Medication effects

The variability in medication status across subjects (see Table 1) provided an opportunity to examine the effects of medication on subcortical activation. Two sets of analyses were performed. The first analysis involved examining group differences (defined as being on or off a certain medication type) in fit coefficients obtained during scan 1 (euthymic or hypomanic state) and then again during scan 2 (depressed state). The second analysis

involved examining group differences on the fit coefficient change score.

Analyses indicated significant effects of medication status for antipsychotics and antidepressants, but not for mood stabilizers on basal ganglia activation. Interestingly, these effects were found for the left-hand trials only and generally when patients were in their depressed state. Results indicated that patients on antidepressants at time of scans ($n=7$) had significantly greater fit coefficients than patients off antidepressants ($n=3$) in several regions including the left thalamus ($t=3.28$; $p=0.011$), left GPe ($t=2.47$; $p=0.038$), right caudate ($t=4.17$; $p<0.003$), and right thalamus ($t=3.03$; $p=0.016$). We found that patients off antipsychotics at time of scans ($n=7$) had significantly greater fit coefficients than patients on antipsychotics ($n=3$) in several regions including the left thalamus ($t=3.89$; $p=0.004$), left putamen ($t=3.60$; $p=0.007$), left GPe ($t=3.11$; $p=0.01$), left GPi ($t=4.64$; $p=0.001$), right caudate ($t=2.46$; $p<0.04$), right putamen ($t=3.38$; $p=0.009$), and the right thalamus ($t=3.77$; $p=0.005$). There were no significant effects of medication status on the fit coefficient change scores.

4. Discussion

There were two key findings of the present study. First, when subjects were in an elevated or euthymic state (scan 1) there were strong positive associations between caudate activation bilaterally and the globus pallidus of the left hemisphere and mood state based on a self-rated scale. Thus, the basal ganglia appear to be more active in subjects reporting elevated mood than in subjects characterizing their mood as euthymic. These findings are consistent with previous functional neuroimaging studies. Investigators have reported increased activity in the caudate during mania in bipolar disorder (O'Connell et al., 1995; Blumberg et al., 2000), particularly in the left hemisphere. While we did not observe a relationship between BOLD responses in basal ganglia and depression severity with the between subjects analysis (possibly due to subject selection bias and small study sample), others have (Baxter et al., 1985; Dunn et al., 2002). Our findings suggest that striatal activity in both hemispheres may be disinhibited during elevated mood states in bipolar disorder.

A second important finding emerged from the within-subject longitudinal analyses. We found an association between an *increase* in severity of depression (based on the mood item of the SMS) and a *decrease* in BOLD activity in the external segment of the right globus pallidus. This finding suggests that the globus pallidus

became less responsive while performing a simple motor task during the depressed phase in bipolar disorder compared to the normal or euthymic state. There have been only a few studies reporting pallidal changes in bipolar disorder. Using PET, Mayberg (2001) reported pallidal hypermetabolism in bipolar depression. Using fMRI, we previously reported no abnormality in pallidal activity in depressed bipolar disorder subjects; however manic bipolar subjects exhibited increased activity in both segments of the left globus pallidus compared to healthy subjects (Caligiuri et al., 2003). Differences in imaging techniques, study design and subject characteristics make it difficult to compare previous studies of pallidal activity with the present findings. Nonetheless, with subjects serving as their own control over genetic, developmental, pharmacologic, and environmental variability the results of the present study implicate a reduction in pallidal activity in bipolar depression.

We found use of certain psychotropic medications to have potentially important effects on subcortical activation during a simple motor task. Opposite effects were found for antipsychotics and antidepressants. Subjects in depressed states taking antidepressants exhibited greater activation in the thalamus, external globus pallidus, and caudate compared to subjects off antidepressants. Conversely, subjects in depressed states taking antipsychotics exhibited less activation in the thalamus, putamen, both segments of the globus pallidus, and caudate compared to subjects off antipsychotics. These findings suggest that antidepressants may produce an activating effect while antipsychotics may produce an opposite effect in subcortical brain regions that can be detected using a simple reaction time motor task. Further research is necessary to address the question of whether fMRI together with a simple reaction time task can be used as a proxy measure to examine the neuroanatomic changes induced by psychotropic medications.

The results from the follow-up analyses suggest different roles for the caudate and globus pallidus in depression. As subjects' self-reported affect decreased over the study period, activation of the GPe *decreased*, whereas activation of the caudate nucleus *increased* during a motor task. These changes were evident in the right hemisphere only. A consideration of the neurochemical and physiologic differences of these two regions of the basal ganglia circuit may shed light on this seemingly paradoxical finding. The striatum and globus pallidus exert inhibitory tone in the regulation of mood and motor function (Alexander and Wickens, 1993; Connolly and Burns, 1993; Tekin and Cummings, 2002). Increased caudate activity (our first observation) could lead to an increase in GABAergic outflow to the external

globus pallidus. This in turn could result in an increase in inhibition of pallidal activity (our second finding) and lead to disinhibition of the subthalamic nucleus. Disinhibition of the subthalamic glutamate leads to an increase in (internal) pallidal activity and subsequent increase in pallido-thalamic inhibition. Reduced thalamocortical excitation may underlie the behavioral changes observed in depression, such as slowed movement, reduced energy, diminished appetite, anhedonia, slowed thinking and speech, and depressed mood.

This present study has limitations. First, we used a non-standard tool to quantify changes in affect across multiple dimensions. It remains uncertain whether the relationships between change in basal ganglia blood flow and symptom change observed in this study would remain if we had utilized standard depression and mania rating scales. However, our goal was to employ a patient-rated instrument that would be brief and sensitive to both manic and depressive symptoms that could be administered moments before undergoing the MRI scan. None of the existing rating scales satisfied these criteria. A second potential limitation pertains to the decision to undertake a ROI rather than a voxel-wise analysis to identify subcortical brain areas mediating symptom change in bipolar disorder. ROI analyses are based on analysis of the mean levels of activation within a specified region, and is vulnerable to response variability. Results may underestimate responses in some important regions because of the measures of central tendency ignore highly responsive voxels. Lastly, interpretation of the major findings of this study with regard to the relationships between affective state and subcortical activation should be made with caution as correlation coefficients are often overestimated in studies of small samples.

Acknowledgments

This research was supported, in part, by grants from the National Alliance for Research on Schizophrenia and Depression (NARSAD), the National Institute of Mental Health (R01 MH57140), the Department of Veteran Affairs Merit Review Program, and the VISN-22 MIRECC.

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