Increased Anterior Cingulate and Caudate Activity in Bipolar Mania

Hilary P. Blumberg, Emily Stern, Diana Martinez, Sally Ricketts, Jose de Asis, Thomas White, Jane Epstein, P. Anne McBride, David Eidelberg, James H. Kocsis, and David A. Silbersweig

Background: Executive control of cognition, emotion, and behavior are disrupted in the manic state of bipolar disorder. Whereas frontal systems are implicated in such dysfunction, the localization of functional brain abnormalities in the manic state is not well understood.

Methods: We utilized a high-sensitivity $H_2^{15}O$ positron emission tomography technique to investigate regions of increased brain activity in mania, compared to euthymia, in bipolar disorder.

Results: The principal findings were manic state-related increased activity in left dorsal anterior cingulate, and left head of caudate.

Conclusions: The findings suggest that the manic state of bipolar disorder may be associated with heightened activity in a frontal cortical–subcortical neural system that includes the anterior cingulate and caudate.

Key Words: Bipolar disorder, mania, affective disorders, tomography emission-computed, gyrus cinguli, caudate nucleus

Introduction

Classic manic symptoms include sustained heightened mood, as well as associated abnormalities in attentional and executive functions, such as distractibility and excessive maladaptive behaviors. There are a number of nonimaging studies suggesting that manic states are associated with greater right than left hemisphere prefrontal and subcortical impairment, and greater ventral than dorsal cortical impairment (reviewed in Bear 1986; Sackeim et al 1982; Starkstein and Robinson 1997; Wexler 1980). Although human brain lesion studies can help to localize regions of decreased functioning, post-lesion compensation and reorganization can complicate the interpretation of findings. Furthermore, the elucidation of dysregulated or heightened activity in associated brain regions, which might also underlie manic symptoms, has been limited by available experimental methods. Functional neuroimaging techniques allow for the investigation, in vivo, of such possible manic state-related abnormalities in regional brain function.

Functional neuroimaging techniques have been applied to a greater extent to the study of depression, than of mania, in mood disorders. Positron emission tomography (PET) studies of depression have demonstrated abnormalities in ventral, rostral and dorsal anterior cingulate cortex (AC), dorsolateral prefrontal cortex, as well as caudate, which receives significant projections from these cortical structures (Baxter et al 1989; Bench et al 1993; DeAsis et al 1999; Drevets et al 1997; George et al 1997; Mayberg et al 1997).

The regional brain involvement in mania is less clear. There are findings that support possible frontal lobe, temporal lobe, and basal ganglia involvement in primary mania, although the associated studies differ in the imaging techniques and normalization procedures used, the delineation of the frontal lobe regions examined, and whether increases or decreases were found in these regions (Table 1).

Decreased anterior–posterior gradients and general frontot activity have been reported in mania (al-Mousawi et al 1996; O’Connell et al 1995; Rubin et al 1995). More specifically, mania-associated increased activity has been reported in dorsal and ventral AC (Drevets et al 1995, 1997; Goodwin et al 1997), and increased activity has been reported in more lateral prefrontal cortices (Baxter et al 1989).

There has been evidence to suggest possible involvement of the temporal polar cortex in mania; however, there have been conflicting findings in this area. Decreased right basotemporal activity has been reported, with a trend toward a negative correlation between mania ratings and...
Table 1. Results of Regional Functional Neuroimaging Studies of Primary Mania in Resting States

<table>
<thead>
<tr>
<th>Group</th>
<th>Technique</th>
<th>n(^a)</th>
<th>Frontal findings</th>
<th>Temporal findings</th>
<th>Basal ganglia findings</th>
<th>Correlation to mania scores</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter et al 1989</td>
<td>FDG PET</td>
<td>6 (6)</td>
<td>Increased left anterolateral compared to depression</td>
<td></td>
<td></td>
<td></td>
<td>Differences may be accounted for by the metabolic reduction in the depressed phase</td>
</tr>
<tr>
<td>Migliorelli et al 1993</td>
<td>HMPAO SPECT</td>
<td>5 (5)</td>
<td>Decreased right basotemporal</td>
<td></td>
<td></td>
<td></td>
<td>All subjects female, normalized to cerebellum</td>
</tr>
<tr>
<td>Drevets et al 1995</td>
<td>FDG PET</td>
<td>3 (3)</td>
<td>Increased right ventral AC</td>
<td>Increased temporal (in 11/11)</td>
<td>Increased right ventral striatum</td>
<td>Positive with right temporal</td>
<td>Abnormalities on visual inspection</td>
</tr>
<tr>
<td>O’Connell et al 1995</td>
<td>IMP SPECT</td>
<td>11</td>
<td>Decreased frontal (in four of 11 subjects)</td>
<td></td>
<td></td>
<td></td>
<td>Preliminary suggestion of left &gt; right rCBF in mania compared to depression in inferior prefrontal cortex</td>
</tr>
<tr>
<td>Rubin et al 1995</td>
<td>rCBF</td>
<td>11</td>
<td>Decreased anterior cortical rCBF in depression and mania</td>
<td></td>
<td></td>
<td></td>
<td>Normalized to the area-weighted mean of all regions of interest</td>
</tr>
<tr>
<td>al-Mousawi et al 1996</td>
<td>FDG PET</td>
<td>15 (2)</td>
<td>Decreased anterior-posterior gradient</td>
<td>Increased right temporal and decreased left amygdala</td>
<td></td>
<td></td>
<td>Subjects manic after lithium discontinuation</td>
</tr>
<tr>
<td>Drevets et al 1997</td>
<td>FDG PET</td>
<td>4 (3)</td>
<td>Increased ventral AC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goodwin et al 1997</td>
<td>EMZ SPECT</td>
<td>7 (7)</td>
<td>Increased dorsal AC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gyulai et al 1997</td>
<td>IMP SPECT</td>
<td>3</td>
<td>Increased right &gt; left anterior temporal (in 2/3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blumberg et al 1999</td>
<td>H(_2)(^{15})O PET</td>
<td>5</td>
<td>Decreased orbitofrontal</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

FDG, 18 fluorodeoxyglucose; PET, positron emission tomography; HMPAO, 99mTc-exametamphetamine oxime; SPECT, single photon emission computed tomography; AC, anterior cingulate; IMP, isopropylthioamphetamine; rCBF, regional cerebral blood flow; EMZ, 99mTc-exametazime.

\(^a\)Numbers in parentheses represent the number of unmedicated subjects.
right basotemporal cerebral blood flow (CBF) (Migliorelli et al 1993); however, increased right temporal activity (al-Mousawi et al 1996; Gyulai et al 1997; O’Connell et al 1995) and decreased left amygdala activity (al-Mousawi et al 1996) have also been reported, and right temporal increases have been shown to positively correlate with mania scores (O’Connell et al 1995). Abnormalities have been reported in bipolar mania in the basal ganglia. There was a report of increased uptake in the basal ganglia, greater in the right hemisphere (O’Connell et al 1995). Another preliminary report suggests that there may be increased right ventral striatal activity (Drevets et al 1995). We previously reported manic state-related decreased orbitofrontal activity (Blumberg et al 1999). We suggested that dysfunction in ventral cortices might be associated with increased activity in associated cortical and subcortical structures with significant connectivity to these regions. As noted above, the nonimaging literature suggests that an imbalance with right more than left, and ventral more than dorsal, frontal lesions are associated with mania. It is plausible that, conversely, increased left dorsal frontal activity may contribute to a similar regional imbalance, in the absence of gross lesions. The small functional neuroimaging literature of mania to date has not resolved these issues. In this article we describe analyses performed to examine increases in brain activity in mania compared to euthymia with particular interest in lateralized frontal systems.

Methods and Materials

Subjects with Bipolar I Disorder, non–rapid-cycling, established by Structured Clinical Interview (First et al 1995) included five manic subjects (M; four female, one male; mean age 34.2 years, SD = 12.2), and six euthymic subjects (E; four female, two male; 32.5 years, SD = 11.0). Manic subjects met DSM-IV criteria for a current manic episode. Euthymic subjects did not meet DSM-IV criteria for a current manic or depressive episode and had a score of <6 on the 29-item Hamilton Depression Rating Scale (Hamilton 1960). Subjects were without comorbid Axis I or II Disorders, except distant substance abuse (>5 years in 3 M, 3 E). All subjects were right-handed (Oldfield 1971), spoke English as a first language, and were without neurologic or medical illness. Patient groups did not differ significantly in estimated premorbid verbal intelligence quotient (Grober and Sliwinski 1991): M = 111.6 ± 6.0, E = 118.7 ± 7.6. The manic and euthymic groups also did not differ significantly in illness duration: M = 14.2 years ± 14.9, E = 12.0 ± 5.6. Subjects denied family history of psychotic or anxiety disorder. Medications included mood stabilizers (lithium [4 M, 5 E], valproic acid [2 M, 2 E], and carbamazepine [1 M, 2 E]), antipsychotic agents (3 M), benzodiazepines (4 M, 1 E), and antidepressants (2 E). No subject required acute sedation for scanning. After complete description of the study to the subjects, written informed consent was obtained in accordance with hospital institutional review board protocols.

A General Electric ADVANCE Positron Emission Tomograph was operated in three-dimensional mode (Lewellen et al 1996). Four scans, in one study session, were performed in the resting condition with eyes closed, lights dimmed, and low levels of ambient noise. Regional cerebral blood flow (rCBF) was measured as an index of local neuronal activity (Raichle 1987). H215O delivery and data acquisition were performed according to a previously published technique (Silbersweig et al 1993). Re-alignment of images across runs within subject was performed to correct for slight head movement, and spatial smoothing (15 mm full-width-at-half-maximum) was performed. Head movement was significantly less than the resolution of smoothing for all subjects. Regional CBF was normalized to a mean of 50 mL/100 gm/min. Group effects were identified with multiple linear regression analysis. Image processing and analyses were performed with statistical parametric mapping (SPM ‘96, Wellcome Department of Cognitive Neurology, University College London, UK) according to the General Linear Model, and probability estimates were determined according to the Theory of Random Fields (Friston et al 1995).

Results

Mean mania scores (Altman et al 1994) for the manic group and the euthymic group were 21.8 ± SD 6.7 and 2.5 ± 4.5, respectively. The groups differed significantly on 7 of the 10 mania items (p < .05; Student’s t test, two
tailed), including measures of mood elevation, irritability, pressured speech, racing thoughts, distractibility, grandiosity, and sleep disturbance. Although there were trends toward increases in mania, there were no significant differences on measures of hyperactivity, increased energy, and impaired judgment. The lack of difference between groups on these items may reflect a bias in selecting manic subjects without psychomotor agitation that would render them unable to complete scanning, and in choosing only those subjects judged by an attending physician to have capacity to make an informed decision to participate in the study.

Increased mania-associated rCBF was detected in the bilateral dorsal AC, the right ventral AC, and in the left head of the caudate at a threshold of \( p < .001 \), uncorrected (Table 2). Applying correction for multiple comparisons, significant findings were restricted to the left dorsal AC and left head of caudate (\( p < .05 \), corrected for multiple comparisons; Figures 1 and 2).

Figure 1. Sagittal section 16 mm left of the midsagittal plane demonstrating increased activity in the head of the caudate, and in left dorsal anterior cingulate in mania, compared to euthymia. Regional cerebral blood flow functional results (\( p < .001 \)) are displayed in color and superimposed on a structural T1-weighted magnetic resonance imaging template.

Figure 2. Mean normalized regional cerebral blood flow (rCBF) for the manic and the euthymic groups in the left dorsal anterior cingulate and caudate. Regional cerebral blood flow values (the Y axis) were normalized to a mean of 50 mL/100 g/min for the manic and euthymic subject groups. Each column corresponds to the mean (±SD) rCBF for a group of subjects. Results for subjects in the manic state are represented in blue, and results for subjects in the euthymic state are represented in red. The two columns on the left are values for the left dorsal anterior cingulate at the statistical parametric mapping (SPM) regional maximum. The two columns on the right are values for the left head of caudate at the SPM regional maximum.
Discussion

DSM-IV criteria for a manic episode include a sustained heightened emotional state, as well as accompanying symptoms of distractibility, rapid loosely connected thoughts, and behaviors associated with increased motivational drives (American Psychiatric Association 1994). We report here greater manic, versus euthymic, state-related activity in the AC and caudate. The greater activity in these structures may relate to behavioral abnormalities observed in mania.

The AC is associated with attentional, emotional, and cognitive functions. The AC has significant reciprocal connections to the amygdala (Vogt et al 1992), a brain structure thought to be central to emotional processing. Stimulation of AC can lead to euphoria and a sense of well-being, as well as alterations in rate, volume, and degree of perseveration in speech (reviewed in Devinsky et al 1995). Cingulate seizures have been associated with ictal emotional changes, and interictal irritability, emotional lability, and sexual behaviors (Devinsky et al 1995). Rats will self-stimulate in this brain region in a manner enhanced over time and thought to be associated with kindling (Corbett and Stellar 1983), a process theorized to develop in limbic brain regions in bipolar disorder. Anticonvulsant agents, also used as mood stabilizing agents in bipolar disorder, have been demonstrated to interfere with this process (Post et al 1982).

The principal finding of this study was in the dorsal region of the AC. This region of the AC has relatively organized and granular cytoarchitecture, and the related behavioral functions are of higher order (Devinsky et al 1995), than the ventral AC. The dorsal AC has been associated with cognitive functions, such as the appropriate directing of attention, conflict monitoring, and response selection (Botvinick et al 1999; Carter et al 1998; Peterson et al 1999; Posner and Rothbart 1998). Decreased activity in the left dorsal AC has been described in association with depressive cognitive abnormalities (Bench et al 1993; DeAsis et al 1999; George et al 1997).

The more ventral regions of the AC region have a more agranular cytoarchitecture and the related functions are more primitive. The ventral AC has efferent connections to autonomic, endocrine, and visceral effectors (Nauta 1971), and is thought to regulate the associated functions. The rostral AC has also been associated with the expression of internal states, including vocalizations and social behaviors (Devinsky et al 1995). The ventral AC region has been demonstrated to activate more to emotional stimuli, in contrast to the dorsal AC, which may activate more during cognitive tasks (Whalen et al 1998). One region of increased activity in this study, the ventral AC, is a region that overlaps that previously reported to have increased activity in mania (Drevets et al 1997), representing a possible convergence of findings.

This study also demonstrated increased activity in the left head of the caudate in mania, ipsilateral to the increased activity in the dorsal AC. The AC has excitatory efferent input to the head of the caudate (Ehlen and Graybiel 1995; Yeterian and van Hoesen 1978). The modulatory caudate input back to the AC has intervening connections via the globus pallidus and thalamus (Alexander et al 1986). The known structural connectivity between the cingulate and caudate suggests that the increased activity occurs within the context of this cortical–subcortical neural system. Increased activity has previously been reported in mania in the basal ganglia (Drevets et al 1995; O’Connell et al 1995) and warrants further investigation.

We speculate that increased AC activity could relate to heightened, dysregulated attentive and cognitive processes, such as manic-type distractibility and maladaptive excessive behaviors. An alternative possible interpretation for increased left AC activity in the manic state relates to the behavioral constraint required during scanning. The scanning requirement of decreasing inappropriate behavioral outputs, such as psychomotor movements and speaking, may require additional efforts on the part of manic subjects. Heightened AC and caudate activity could be associated with this demand.

The findings here are preliminary and require replication, as this study is limited by the relatively small number of subjects and their medication status. More manic subjects were receiving both antipsychotic and benzodiazepine medications, and more euthymes were receiving antidepressants. In each group all but one subject was on lithium at the time of study. Goodwin et al (1997) reported decreases in anterior cingulate and right caudate CBF after lithium withdrawal, whereas development of mania on lithium withdrawal was associated with increased AC CBF. There have been reports of increased caudate activity and basal ganglia size associated with antipsychotic medication (Buchsbaum et al 1987; Chakos et al 1994; Holcomb et al 1996), and decreased rostral AC activity with antidepressant treatment (Mayberg et al 1997); however, there is not clear evidence to suggest a contribution to the lateralized effects seen in this study. Both antipsychotic and benzodiazepine medication have been reported to be associated with decreased AC activity (Holcomb et al 1996; Veselis et al 1997), which would have predicted the opposite outcome in the AC in the manic group. Findings in ventral AC and striatum have previously been reported in three unmedicated manic subjects, although the results were lateralized to the right hemisphere (Drevets et al 1995).

Increased anterior cingulate activity is not specific to
bipolar manic states. Elevated emotional states in healthy subjects have been reported in association with increased AC activity. For example, Ketter et al (1997) demonstrated increased rCBF in AC associated with procaine-induced euphoria in healthy subjects. In a study of transient psychologically induced emotional states (via emotional memory and face presentation) also in healthy subjects, AC rCBF has been demonstrated to increase significantly in sad states, and there was a trend toward an increase in happy states (George et al 1995). Increased anterior cingulate activity is also not specific to the bipolar diagnosis, and has also been demonstrated in symptomatic states of anxiety disorders, such as obsessive-compulsive disorder and phobias (Rauch et al 1994, 1995). These and our findings, seen in the light of the behavioral neuroscience literature, suggest that the AC is a vulnerable part of an important final common pathway of emotional regulation.

As this study was designed to examine relative regional changes in CBF, mean CBF measures were normalized for each subject, and global changes were not assessed. There has been a previous report to suggest possible global brain changes in mania. Kishimoto et al (1987), reported generalized increases in 11C-glucose uptake in three medication-free manic patients compared to control subjects. Other groups have not found an increase in global activity (Rubin et al 1995; Schwartz et al 1987; Silfverskiold and Risberg 1989).

Concurrent volumetric measurements were not performed in this study. A possible contribution of dorsal AC volume change across mood states can be a subject for further study. There have been reports of volumetric differences in ventral AC grey matter (Drevets et al 1997), and a conflicting literature on the possibility of dorsal AC volume abnormalities in mood disorders (Aylward et al 1994; Dupont et al 1995; Krishnan et al 1992; Lenze and Sheline 1999). This literature suggests possible trait abnormalities; however, volumetric state abnormalities that would have greater implications for the current work are less clear.

The most significant areas of increased manic state-related activity were in the left dorsal AC and head of caudate. This finding, and our previously reported finding of decreased orbitofrontal activity in mania (Blumberg et al 1999), are consistent with theories that relative right lower than left, and ventral less than dorsal, prefrontal activity is associated with manic states (Bear 1986; Sackeim et al 1982; Starkstein and Robinson 1997; Wexler 1980). This has been theorized to extend to relative impairment in activity in related right hemisphere subcortical structures, including caudate, thalamus, and medial diencephalon (Mega et al 1997; Starkstein and Robinson 1997). Much of the reasoning for these theories is based upon manic behavior described in association with brain lesions. The data in this functional neuroimaging study suggest that greater left dorsal AC and caudate activity may contribute to an equivalent net imbalance in brain function associated with the manic state in bipolar disorder.

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