Psychiatry Research: Neuroimaging 181 (2010) 136–140

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Metabolic evidence of corticolimbic dysregulation in bipolar mania

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ARTICLE INFO

Article history:
Received 18 July 2008
Received in revised form 2 June 2009
Accepted 28 August 2009

Keywords:
Bipolar disorder
Bipolar depression
Tomography, emission-computed
PET
Mania

ABSTRACT

Findings from previous research on the neural substrates of mania have been variable, in part because of heterogeneity of techniques and patients. Though some findings have been replicated, the constellation of neurophysiological changes has not been demonstrated simultaneously. We sought to determine resting state cerebral metabolic changes associated with relatively severe acute mania. Resting positron emission tomography with ^{18}fluorodeoxyglucose was performed in bipolar disorder patients with severe mania and in healthy controls. Statistical parametric mapping was used to determine regions of differential metabolism. Relative to controls, bipolar disorder patients with mania exhibited significantly decreased cerebral metabolism in both the dorsolateral prefrontal regions and the precuneus. Conversely, manic patients exhibited significant hypermetabolism in the parahippocampal complex, temporal lobe, anterior cingulate, and subgenual prefrontal cortex compared with controls. These results demonstrate simultaneous resting limbic/paralimbic hypermetabolism and prefrontal hypometabolism during mania. The findings support the hypothesis of corticolimbic dysregulation as a crucial contributor to the pathophysiology of bipolar disorder.

1. Introduction

The corticolimbic network comprises a dorsolateral prefrontal circuit that originates in Brodmann's Area (BA) 9 and 10, an orbitofrontal circuit originating in BA 10 and 11, and an anterior cingulate circuit that originates in BA 24 (Mega and Cummings, 1994). There is growing evidence that corticolimbic dysregulation (Brooks et al., 2009a; Adler et al., 2006; Strakowski et al., 2005) may be a crucial contributor to the pathophysiology of bipolar disorder. Metabolic dysregulation has been found to persist across depression and euthymia, with less clear findings regarding mania. For example, in unmedicated patients with bipolar depression, there is evidence of prefrontal, anterior cingulate, and insula hypometabolism relative to healthy controls (Brooks et al., 2009a,b, 2009). Older patients with bipolar disorder have demonstrating relations between resting prefrontal hypometabolism and amygdala hypermetabolism and delayed verbal recall (Brooks et al., 2009).

Cerebral blood flow and metabolic studies in mania have not often been replicated, but have reported differences in prefrontal and paralimbic structures. Blumberg et al. (2000) reported a resting cerebral blood flow study that revealed increased blood flow in the anterior cingulate of manic patients relative to controls. Analogous results were obtained with a decision-making task, which was associated with increased metabolism in paralimbic and other medial temporal structures in manic patients (Rubinsztein et al., 2001). Resting hypometabolism has been reported in the medial (Rubinsztein et al., 2001), dorsolateral (al-Mousawi et al., 1996), and subgenual (Drevets et al., 1997) prefrontal cortex. There is some evidence of decreased resting amygdala metabolism (al-Mousawi et al., 1996) in one study and conflicting evidence regarding differences in temporal metabolism with one report of resting hypermetabolism (O'Connell et al., 1995) and one of resting hypometabolism (Migliorelli et al., 1993).

Previous cerebral metabolic studies have not provided a clear picture of corticolimbic dysregulation in mania. Although there have been several reported findings of prefrontal hypometabolism, these regions have not had much overlap and the majority of these findings were not replicated from study to study, even among resting studies. No cerebral metabolic study of mania has demonstrated simultaneous paralimbic hypermetabolism and prefrontal hypometabolism. A corticolimbic dysregulation model of bipolar disorder (Brooks et al., 2009a,b, 2009) would lead us to predict that manic patients would exhibit prefrontal hypometabolism in the face of limbic hypermetabolism. The nature of differences in paralimbic structures such as the subgenual prefrontal cortex are more challenging to predict, but based on previous findings (Drevets et al., 1997), we would expect areas of hypermetabolism.

In this study, we attempted to capture simultaneous limbic/paralimbic hypermetabolism and prefrontal hypometabolism in resting positron emission tomography (PET) scans in a group of minimally medicated severely manic patients. Though it would be desirable to obtain these scans from unmedicated patients, for ethical, logistical, and clinical reasons, this is seldom feasible. Thus, we

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doi:10.1016/j.pscychresns.2009.08.006

obtained scans within 3 days of admission to an acute psychiatry unit with no more than 3 days of medication.

2. Methods

2.1. Subjects

The Stanford University Administrative Panel on Human Subjects approved this study; all participants provided verbal and written informed consent before enrollment.

2.1.1. Manic patients

Demographic information for the bipolar disorder patients is provided in Table 1. All patients had been recently admitted to an acute psychiatry unit and met DSM-IV criteria for bipolar disorder type I, current manic episode based on a semi-structured clinical interview performed by a psychiatrist. One patient had an additional diagnosis of cocaine dependence in remission, two had an additional diagnosis of post-traumatic stress disorder, and one had an additional diagnosis of gender identity disorder, not otherwise specified.

Patients were required to have a Young Mania Rating Scale (Young et al., 1978) score of at least 25 at the time of the PET scan, and overall scores ranged from 29 to 41. Manic patients were scanned during the first 3 days of hospitalization. One patient was unmedicated at the time of the scan. The remaining patients were receiving monotherapy with olanzapine ($n=5$), quetiapine ($n=1$), or aripiprazole ($n=1$), which they had received for no more than 3 days before the scan. The medication regimen was not uniform because of individual patient preferences. All patients had been medication noncompliant prior to the time of admission.

2.1.2. Healthy controls

The eight age- and gender-matched participants in the healthy control group were volunteers recruited from the community through advertisements. The control participants did not meet DSM-IV criteria for any affective or psychotic disorder as determined by the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and none was taking any psychotropic medication. Healthy controls had an average age of 55.9 years, 16.4 years of education, and an average YMRS score of 0.25. As in the bipolar disorder group, seven were male and one was female. There were no meaningful differences between healthy controls and patients regarding age, gender, education, and handedness.

2.1.3. Exclusion criteria

Participants were excluded from the study if they had any of the following conditions: seizure disorder; progressive neurological and/or systemic disorder; any implanted metal; significant unstable concurrent medical illness (history of hypothyroidism or hyperthyroidism was permissible if treated and if the participant had normal blood thyroid stimulating hormone concentration); administration of benzodiazepines within 24 h of the scan, stimulants, steroids; hormone replacement therapy; electroconvulsive or light therapy; administration of any investigational drug within 30 days prior to screening; alcohol abuse within the 2 weeks prior to screening; drug abuse less than 1 month prior to screening; pregnancy or breastfeeding; or incapacity to consent to study procedures.

Table 1
Demographic information for bipolar disorder patients.

Patient	Age	Gender	Handedness	Education	YMRS	Psychosis
1	49	Male	Right	19	32	6
2	46	Female	Right	16	32	4
3	50	Male	Right	16	41	8
4	55	Male	Right	10	33	4
5	57	Male	Right	18	29	6
6	58	Male	Right	13	37	8
7	46	Male	Missing	Missing	39	6
8	61	Male	Left	21	30	6
Average	52.8	–	–	16.4	34.1	6.0

Note: YMRS = Young Mania Rating Scale. Psychosis is item #8 from the YMRS, which measures psychosis on a scale from 0 to 8. "Missing" indicates missing data.

2.2. PET acquisition

Positron emission tomography scans with fluorodeoxyglucose (FDG) were acquired on a Siemens Exact 921 scanner, which obtains 69 tomographic slices with an in-plane full-width half-maximum resolution of 7 mm, and an axial resolution (slice thickness) of 5 mm at the center of the gantry. Subjects were scanned after at least 6 h of fasting to increase FDG uptake by the brain and reduce intrascan blood glucose variability. Ten mCi of FDG was injected intravenously after subjects were instructed to relax and rest with their eyes closed in a darkened room. They were further instructed not to engage in mental activities apart from passively attending to their current emotional and sensory experiences during the 30-min FDG uptake period. Clinical personnel waited outside the room to help ensure compliance and safety.

Intrascan head movement was restricted by use of foam headrests and light restraints placed upon the chin and forehead. Subjects' eyes were covered, and the PET gantry was aligned to the canthomeatal line. Emission data were obtained for 15 min following uptake. A ^{68}Galium rotating pin source was used to obtain a 5-min transmission scan to correct for photon attenuation of emission data.

2.3. Image processing

Image processing was performed using Statistical Parametric Mapping (SPM5, Update 826) software (www.fil.ion.ucl.ac.uk/spm). All images were stereotactically normalized to the Montreal Neurological Institute (MNI) template provided with SPM5 through a 12-parameter affine transformation and nonlinear warping with basis functions (Ashburner, and Friston, 1999). Whole brain metabolic activity was calculated for each image as the mean of all voxels greater than the background threshold of 1 of the mean of the image space. Each image was subjected to proportionate scaling to normalize values across images. Gray matter was thresholded at 80% of each subject's mean whole brain metabolic activity. The normalized images had 2-mm isotropic voxels and were smoothed with a 12-mm Gaussian kernel. An intensity threshold of $P<0.005$ (uncorrected) and a spatial extent threshold of 50 voxels were applied as in prior studies (Brooks et al., 2009a,b, 2009). Correlation analyses were performed using the same intensity and extent thresholds. For ease of localization, the MNI coordinates provided by SPM5 were converted to Talairach (Talairach and Tournoux, 1988) space using the Talairach demon and Wake Forest University PickAtlas (Maldjian et al., 2003).

3. Results

3.1. Regions of hypometabolism in mania

The statistical parametric map of regions of hypometabolism in manic patients relative to healthy controls is provided in Fig. 1, and the coordinates of the regions are provided in Table 2. The manic group of patients demonstrated significant hypometabolism in the dorsolateral prefrontal cortex in Brodmann's Areas (BA) 9, 10, and 46. There were significant hypometabolic regions in the dorsal anterior cingulate (BA 32) and the precuneus (BA 7). Finally, there was a region of hypometabolism in the superior temporal cortex (BA 22; not illustrated in the figure).

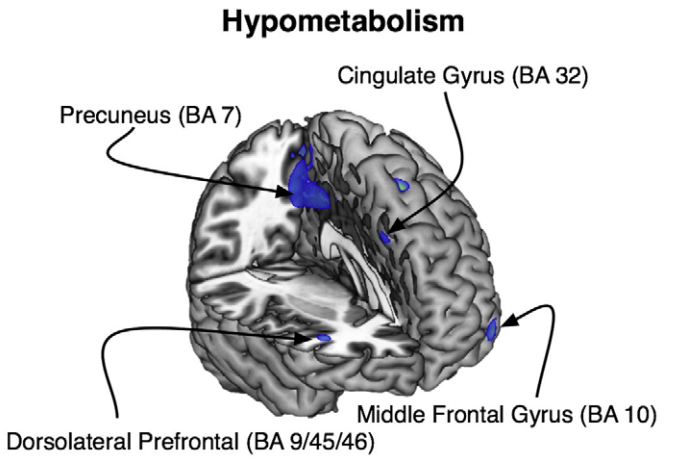

Fig. 1. Regions of decreased cerebral metabolism in manic patients relative to healthy controls.

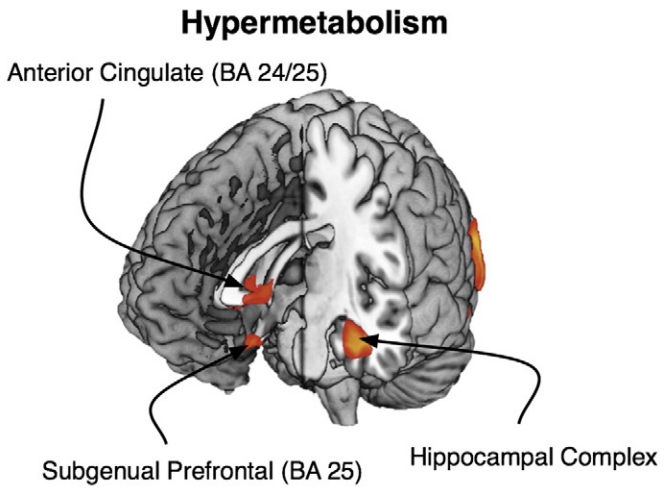

Fig. 2. Regions of increased cerebral metabolism in manic patients relative to healthy controls. Note that apparent misalignment of some regions is a result of superimposition on the template for display purposes.

3.2. Regions of hypermetabolism in mania

Regions of hypermetabolism in manic patients relative to healthy controls are illustrated in Fig. 2, and the coordinates are provided in Table 2. Manic patients exhibited hypermetabolism in the left hippocampal complex, the rectal gyrus (BA 25; part of the subgenual prefrontal region), and bilateral inferior temporal regions. There was also a region of hypermetabolism extending from the ventral anterior cingulate (BA 24) to the head of the caudate.

4. Discussion

In this study, we reported resting cerebral metabolic differences associated with mania, and were able to demonstrate simultaneous prefrontal hypometabolism and limbic/paralimbic hypermetabolism, which supports the hypothesis that corticolimbic dysregulation is a crucial contributor to the pathophysiology of bipolar mania. When the present findings are considered in the context of previous work, the metabolic picture of mania that emerges is one of paralimbic hypermetabolism that is not effectively modulated, perhaps because of dorsolateral prefrontal hypometabolism. Increased limbic and paralimbic metabolism during mania could represent a deficit of emotion regulation.

Previous neuroimaging studies of mania are summarized in Table 3, which highlights the variability of findings as well as the differences in degree of mania, sample size, and the type of neuroimaging performed. Perhaps because our sample comprised severely manic patients who were minimally medicated, we were able to detect differences in cerebral metabolism that help unify previous findings. Our findings of hypometabolism in prefrontal regions provide contemporaneous replication and extension of previous findings of decreased resting prefrontal metabolism and blood flow in mania (al-Mousawi et al., 1996; Blumberg et al., 1999).

Besides replicating previous reports of increased dorsal cingulate resting blood flow (Blumberg et al., 2000; Goodwin et al., 1997) and increased resting blood flow in the head of the caudate (Blumberg et al., 2000), we have also replicated Drevets et al.'s (1997) finding of resting subgenual prefrontal cortex (SGPFC) hypermetabolism in mania. As apparent in Table 3, not all studies have found SGPFC hypermetabolism, although some reported resting state hypometabolism in adjacent areas such as the ventral anterior cingulate cortex (Goodwin et al., 1997). In a functional magnetic resonance imaging (fMRI) study using a facial emotional expression rating task, medicated manic patients exhibited decreased SGPFC activation (Lennox et al., 2004), which could be consistent with dampening of a region of increased activity at baseline.

As in previous studies, we did not find evidence of differential resting amygdala metabolism in manic patients relative to healthy

Table 2
Regions of statistically significant hypo- and hypermetabolism in manic patients compared to healthy controls.

Region	BA	Hemisphere	Talairach coordinates			Cluster size	*t*
			x	*y*	*z*		
Hypometabolism							
Superior frontal gyrus/dorsal anterior cingulate gyrus	8/32	Left	−20	8	53	593	5.30
Precuneus	7	Bilateral	−12	−76	34	2588	4.78
Superior temporal gyrus	22	Left	67	−58	10	249	4.27
Middle frontal gyrus	10	Left	−46	50	−8	70	4.25
Inferior frontal gyrus	46	Right	40	33	0	85	4.08
Middle/Inferior frontal gyrus	9/45	Right	44	15	31	92	3.75
Uncus	20	Left	26	−19	−29	65	3.69
Hypermetabolism							
Middle occipital gyrus		Left	−44	−79	13	654	5.20
Inferior temporal and fusiform gyri	37	Right	34	−66	−2	630	4.35
Parahippocampal gyrus/superior and middle temporal gyri	21/38	Left	−34	−14	−16	928	4.33
Inferior temporal and fusiform gyri	37	Left	−57	−58	−4	137	3.72
Middle/inferior/superior temporal gyri	21/38	Right	59	3	−24	263	3.65
Rectal gyrus (subgenual prefrontal)	25	Right	6	12	−26	91	3.60
Ventral anterior cingulate/head of caudate/lentiform nucleus	24	Bilateral	2	10	21	343	2.89

Note: for all *t*'s, $P<0.005$. Cluster size is expressed as number of voxels. BA = Brodmann's area.

Table 3
Summary of neuroimaging studies of mania.

Study	Mania *N*	Mania rating	Findings in manic patients	Modality	Task	Medication status
Baxter et al. (1989)	6	22[a]	↑ Lateral PFC relative to depressed	^{18}FDG-PET	Resting	UM × 1 week
Drevets et al. (1997)	4	20	↑ SGPFC	^{18}FDG-PET	Resting	UM > 4 weeks
al-Mousawi et al. (1996)	15	?	↑ R temporal ↓ bilateral DLPFC ↓ L amygdala	^{18}FDG-PET	Resting	AP, MS
Rubinsztein et al. (2001)	6	25	↓ VMPFC ↑ ACC (32)	^{18}FDG-PET	Decision-making	UM = 1; Li, CBZ, VPA, AP
Goodwin et al. (1997)	7	20[b]	↑ Dorsal and ventral AC	^{99m}Tc EMZ-SPECT	Resting	After Li withdrawal
Gyulai et al. (1997)	2	24	––––––––––––––[c]	^{123}IMP-SPECT	Resting	UM or Li
O'Connell et al. (1995)	11	27	↑ R temporal	^{123}IMP-SPECT	Resting	
Migliorelli et al. (1993)	5	20[d]	↓ R basotemporal	^{99m}Tc HMPAO-SPECT	Resting	UM = 3; AD, MS
Blumberg et al. (1999)	5	22	↓ R middle frontal gyrus ↓ R orbitofrontal gyrus ↓ left dorsal ACC	$H_2^{15}O$-PET	Word generation	MS, BZD, AP, AD
Blumberg et al. (2000)	5	22[e]	↑ L dorsal ACC ↑ L head of caudate	$H_2^{15}O$-PET	Resting	Li, VPA, CBZ, AD, AP, AD
Silfverskiöld and Risberg (1989)	27	?	No change in mean CBF	^{133}Xe-SPECT	Resting	AD, Li, MS, BZD
Rubin et al. (1995)	11	60[b]	↑ L rCBF relative to depressed	^{133}Xe-SPECT	Resting	UM = 10; CH
Benabarre et al. (2005)	7	19[f]	––––––––––––––[c]	^{99m}Tc HMPAO-SPECT	Resting	UM
Altshuler et al. (2005a)	9	15	↑ L amygdala	fMRI	Matching task	UM = 2; Li, VPA, AP
Altshuler et al. (2005b)	11	17	↓ R orbitofrontal ↓ R hippocampus, ACC	fMRI	Go/no go	UM = 4; Li, VPA, AP
Blumberg et al. (2003)	7	19[b]	↓ R ventral prefrontal[c]	fMRI	Stroop	Li, AD, AP, BZD
Caligiuri et al. (2003)	9	> 5[h]	––––––––––––––[c]	fMRI	Reaction time	AP
Chen et al. (2006)	8	24	↑ L fusiform gyrus ↓ amygdala	fMRI	Facial recognition	Li, CBZ, VPA, AP
Elliott et al. (2004)	6	28[g]	↓ orbitofrontal ↑ L VLPFC	fMRI	Emotional go/no go	UM = 1; Li, VPA, AP, BZD
Foland et al. (2008)	9	15	?Bilateral orbitofrontal ?L amygdala[c]	fMRI	Emotional face matching	UM = 2, Li, VPA, AP
Lennox et al. (2004)	10	28	↓ Parahippocampal gyrus ↓ ACC ↓ SGPFC ↑ amygdala ↑ posterior cingulate ↑ L insula ↑ caudate	fMRI	Emotional face rating	Li, VPA, CBZ, AP

Note: Young Mania Rating Scale (YMRS) was used in all studies except where specified.
Li = lithium, CBZ = carbamazepine, VPA = sodium divalproex or valproic acid; MS = mood stabilizer, unspecified; BZD = benzodiazepines; AP = antipsychotic; AD = antidepressant; CH = chloral hydrate; UM = unmedicated.
PFC = prefrontal cortex; ACC = anterior cingulate cortex; SGPFC = subgenual prefrontal cortex; VMPFC = ventromedial prefrontal cortex; CBF = cerebral blood flow.
[a] Authors state that all patients met DSM-III criteria for manic episodes, but report a range of YMRS scores of 5–35.
[b] Modified Mania Rating Scale.
[c] Analyses collapsed across mania and hypomania.
[d] Bech Mania Scale.
[e] Clinician Administered Rating Scale for Mania.
[f] Mania was specified as YMRS > 20, yet analyses were collapsed across mania and hypomania.
[g] One hypomanic subject was used in the analyses. YMRS scores ranged from 13 to 49.
[h] The authors did not specify a mean score; maximum YMRS was 16 and any subject with a score > 5 was classified as "manic".

controls, although we did find hypermetabolism in the adjacent hippocampal complex. Previous evidence of differences in amygdala function during mania is somewhat variable, with one study reporting decreased resting amygdala metabolism in mania (al-Mousawi et al., 1996). A recent fMRI study that used an affective task provided evidence of increased limbic activation and decreased prefrontal activation (Foland et al., 2008), in keeping with the metabolic findings of the present study. Interestingly, although we did not find evidence of resting amygdala hypermetabolism, fMRI studies have revealed increased amygdala activation (Altshuler et al., 2005a; Foland et al., 2008). Perhaps, increased amygdala reactivity is detectable only during emotional tasks (Chen et al., 2006; Foland et al., 2008; Lennox et al., 2004), as opposed to resting states.

4.1. Study limitations

There are some limitations of our study. Our sample size, while larger than some previous studies of mania, was limited. Consequently, we may not have had sufficient power to detect more subtle cerebral metabolic changes that could occur in mania. In addition, all but one of our patients were medicated when they were scanned, although we did not include any patients who had received more than 3 days of medications or benzodiazepines within 24 h of scanning in an attempt to minimize any effects that medications would have on our findings. Studies of the effects of second-generation antipsychotics on cerebral metabolism are few, but there is some evidence that olanzapine is associated with increased prefrontal metabolism (Buchsbaum et al., 2007; Molina et al., 2005). If prefrontal metabolic increases occur with second-generation antipsychotics and occur early in the treatment of bipolar mania, then our findings may underestimate the actual resting prefrontal hypometabolism.

5. Conclusions

The present data provide evidence of corticolimbic dysregulation during mania. Though within-subject data are lacking, when the present results are considered in conjunction with previous findings of altered cerebral metabolism in bipolar disorder during periods of euthymia and mania, it may be that baseline perturbations in corticolimbic function contribute to inter-episode functional deficits.

Severe dysregulation of corticolimbic structures may result in more severe neurocognitive deficits and accompanying clinical symptoms.

Acknowledgements

This research was supported in part by the Medical Research Service of the Veterans Affairs Palo Alto Health Care System (JB, JH).

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