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Corticolimbic metabolic dysregulation in euthymic older adults with bipolar disorder

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Abstract

The corticolimbic dysregulation hypothesis of bipolar disorder suggests that depressive symptoms are related to dysregulation of components of an anterior paralimbic network (anterior cingulate, anterior temporal cortex, dorsolateral prefrontal cortex, parahippocampal gyrus, and amygdala) with excessive anterior limbic activity accompanied by diminished prefrontal activity. In younger patients, such abnormalities tend to resolve with remission of depression, but it remains to be established whether the same is true for older patients. This was a cross-sectional, between-subjects design conducted with 16 euthymic, medicated patients with bipolar disorder (10 type I, six type II) and 11 age-matched healthy controls. All participants were over age 50. Our main outcome measures were relative rates of cerebral metabolism derived from a resting ¹⁸fluorodeoxyglucose positron emission tomography scan in specified regions of interest in the corticolimbic network. Resting metabolic rates in bipolar patients were significantly greater than in controls in bilateral amygdalae, bilateral parahippocampal gyri, and right anterior temporal cortex (BA 20, 38); they were significantly lower in bipolar patients than in controls in the bilateral dorsolateral prefrontal cortices (BA 9, 10, 46). The evidence of corticolimbic dysregulation observed is consistent with the hypothesis that bipolar disorder entails progressive, pernicious neurobiological disruptions that may eventually persist

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Contributors

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during euthymia. Persistent corticolimbic dysregulation may be related to residual affective, behavioral, and cognitive symptoms in older patients with bipolar disorder, even when not experiencing syndromal mood disturbance.

Keywords

Bipolar disorder; Bipolar depression; Tomography; Emission-computed; PET; Prefrontal; Limbic; Hippocampus

1. Introduction

Patients with bipolar disorder spend approximately half of the time in euthymic states, during which not struggling with syndromal affective symptoms, still experience cognitive (Dias et al., 2008; Gildengers et al., 2007, 2004) and functional (Gildengers et al., 2007; Depp et al., 2005; Gupta et al., 2007) deficits. Neurobiological and neurocognitive changes during manic and depressed episodes of bipolar disorder are better established than those during euthymia. Most functional neuroimaging studies suggest that abnormalities during affective episodes tend to attenuate or resolve during euthymia, although a few studies have demonstrated differences between euthymic bipolar patients and healthy controls while engaged in various cognitive tasks (Strakowski et al., 2005a, 2004; Wessa et al., 2007; Deckersbach et al., 2005; Lagopoulos et al., 2007; Lagopoulos and Malhi, 2007; Adler et al., 2004; Monks et al., 2004). However, neuroimaging studies demonstrating *resting state* differences in euthymic bipolar disorder patients are generally lacking. Knowledge of abnormalities during euthymia – especially related to resting state neuroimaging findings in bipolar disorder patients – may advance our understanding of underlying neurobiological changes.

The corticolimbic dysregulation theory of depression (Seminowicz et al., 2004; Mayberg et al., 1999; Mayberg, 1997) posits increased ventral paralimbic activity in conjunction with decreased dorsal cortical activity as a mechanism of depression. This explanation overlaps with integrative literature reviews (Adler et al., 2006; Strakowski et al., 2005b; Ketter et al., 2002), which have advanced the hypothesis that corticolimbic network dysregulation can account for the expression of bipolar disorder in part because of decreased prefrontal modulation of overactive limbic structures. Fig. 1 depicts the corticolimbic network (Strakowski et al., 2005b) with areas of altered metabolism during affective episodes. As Strakowski et al. (2005b) suggested, affect may be related to hypothalamic function, whereas behavior may be related to activity in circuits terminating in the thalamus. Cognition may be related to activity in a pathway involving the anterior cingulate cortex (ACC). Interestingly, many of the structures associated with affective and behavioral alterations in bipolar disorder (including the dorsolateral, ventrolateral, medial orbitofrontal, and subgenual cortices, as well as the hippocampal complex) are also associated with specific neurocognitive functions (Adler et al., 2006). This suggests that corticolimbic dysregulation may provide a parsimonious explanation of the neural substrates involved in diverse aspects of bipolar disorder.

¹⁸Fluorodeoxyglucose positron emission tomography (FDG-PET) provides a measure of cerebral metabolic changes that could complement other evidence supporting the corticolimbic dysregulation hypothesis. Though studies of patients with bipolar disorder demonstrating differences in activation during cognitive tasks are informative, it is unclear whether these differences are task-specific and fail to occur at rest. Arguably, group differences observed in the resting state represent a more generalized finding for this disorder. Furthermore, studying patients in the euthymic state aids in understanding the neurobiology of trait characteristics not influenced by abnormal mood states. For example, it is possible that corticolimbic dysregulation arises only when patients are in altered mood states, with a return to normal

during euthymia. Thus, the study of the euthymic state is vital for understanding trait, as opposed to state, neurobiological aspects of bipolar disorder.

Older adults with bipolar disorder may be an opportune sub-population in which to demonstrate corticolimbic dysregulation at rest during euthymia. Older adults with bipolar disorder may be more likely to have residual neurobiological abnormalities as well as age-related cognitive changes. Thus, older adults could provide a population that allows for increased sensitivity to detect cerebral metabolic changes during euthymia. We hypothesized that in euthymic older adults with bipolar disorder we would find differences in resting cerebral metabolism in areas with prominent corticolimbic dysregulation during depression.

2. Methods

2.1. Participants

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

2.1.1. Bipolar disorder patients—Participants included 16 outpatients diagnosed with bipolar disorder (10 type I, 6 type II) who were recruited from the community through advertisements. All patients were at least age 50 at the time of testing and were clinically evaluated to meet DSM-IV criteria for Bipolar Disorder and to be currently euthymic. One patient was medication-free and the remaining patients were taking standard pharmacotherapy including lithium ($n = 5$), lamotrigine ($n = 5$), divalproex ($n = 1$), antidepressants ($n = 6$), and atypical antipsychotics ($n = 7$). With respect to medication combinations, six were taking one medication, five were taking two medications, and three were taking three medications. Five patients had a history of substance use disorders (alcohol, cocaine, and polysubstance dependence) that had been in remission an average of 12.4 years ($SD = 9.7$). Demographic information for the bipolar disorder patients is provided in Table 1.

2.1.2. Healthy controls—The 11 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, psychotic, or substance use disorder nor were they taking any psychiatric medications. Demographic information for healthy controls is also provided in Table 1.

2.1.3. Exclusion criteria—Participants were excluded from the study if they had any of the following conditions: seizure disorder; progressive neurological disorder; any implanted metal; significant unstable concurrent medical illness; other major Axis I diagnoses; a syndromal affective episode within 30 days of the study; administration benzodiazepines, stimulants, and steroids; hormone replacement therapy; electroconvulsive or light therapy; administration of any investigational drug in the 30 days prior to screening; alcohol abuse within the two weeks prior to screening; drug abuse less than six months prior to screening; pregnancy or breastfeeding; or incapacity to consent to study procedures. Participants were excluded if they had a score on the Young Mania Rating Scale (YMRS) (Young et al., 1978) or the Montgomery-Åsberg depression rating scale (MADRS) (Montgomery and Åsberg, 1979) greater than 10.

2.2. Image acquisition and processing

PET scans were acquired on a Siemens Exact 921 scanner, which yields 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 fasted for at least 6 h prior to the scan to increase FDG uptake by the brain and reduce intrascan blood glucose variability. 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. A ^{68}Ga rotating pin source was used to obtain a 20-minute transmission scan to correct for photon attenuation of emission data. Subjects were instructed to relax and to avoid any active mental processes, aside from passively attending to their current emotional and sensory experiences prior to and during the first 30 min after the intravenous injection of 10 mCi FDG. Emission data were obtained for 30 min following radioisotope uptake.

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 1/8 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.

For the primary analyses, we generated region of interest (ROI) masks using Wake Forest University (WFU) PickAtlas (Maldjian et al., 2003) to provide a standardized approach for spatially normalized images. We used the regional BA descriptions provided by Adler et al. (2006) to provide *a priori* definitions of our ROI. In this way, we created masks for amygdala, parahippocampal gyrus, anterior temporal cortex (BA 20 and 38), subgenual prefrontal cortex (SGPFC; BA 25), cerebellar vermis, medial orbitofrontal cortex (BA 11), ventrolateral prefrontal cortex (BA 10 and 47), dorsolateral prefrontal cortex (DLPFC; BA 9, 10, 46), anterior cingulate (ACC; BA 24 and 32), thalamus, and hypothalamus. With the exception of the cerebellar vermis, which crossed the midline, separate masks were made bilaterally for ROI's. Because our FDG-PET images had undergone Gaussian smoothing, we applied a dilation factor of one in 3D mode to the ROI's in PickAtlas. The masks were then used to extract the ROI from the individual scans using MarsBar (Brett et al., 2002). A between-groups *t*-test was performed on the average values of the voxels in each ROI using SPM5.

In order to assess any other group differences not captured by the *a priori* specified ROI analyses and to confirm the results of the primary analysis, we performed a secondary exploratory analysis in which the whole brain was assessed on a voxel-by-voxel basis. An intensity threshold of $P < .005$ (uncorrected) and a spatial extent threshold of 50 voxels were applied. As in our primary analyses, all images were processed using SPM5 for preprocessing and group level statistics. For localization, the MNI coordinates were converted to Talairach space (Talairach and Tournoux, 1988) using WFU PickAtlas.

3. Results

The results of the primary ROI analyses are provided in Table 2. We found significantly greater cerebral metabolism in the bipolar group relative to healthy controls bilaterally in the amygdala (left: $P < .05$; right: $P < .01$), the right anterior temporal cortex ($P < .05$), and bilateral parahippocampal gyri ($P < .01$). The difference in metabolism in the cerebellar vermis fell short of statistical significance ($P = .06$). All regions with significantly greater cerebral metabolism in bipolar patients were within limbic and paralimbic structures; no prefrontal regions exhibited statistically significant greater metabolism in the bipolar group compared to the control group.

The greater limbic metabolism in patients with bipolar disorder compared to healthy controls was complemented by lower metabolism in bilateral dorsolateral prefrontal cortices (left: $P < .$

05; right: $P < .01$). Differences in metabolism in the bilateral ventromedial prefrontal cortices ($P = .06$) and subgenual prefrontal cortices (left: $P = .10$; right: $P > .10$) did not reach statistical significance. Table 2 also includes the effect sizes averaged across bilateral regions in terms of Cohen's d (Cohen, 1977). Based on this measure, all of the statistically significant effect sizes would be classified as large ($d > 0.5$).

Next, we conducted secondary analyses in which we generated statistical parametric maps of the group differences. This was performed as the prescribed ROI's may have excluded some areas of significance. Given the novelty of the findings, we felt it important to provide as comprehensive a picture as possible of the differences. The results of the SPM analysis comparing bipolar patients and healthy controls are depicted in Fig. 2 and the regions of significant hypo- and hypermetabolism are provided in Table 3. Areas of relatively greater or lesser metabolism in this secondary voxel-based analysis confirmed the findings of the primary analyses, and provide a graphic depiction of the regional extent of actual differences between the bipolar and control groups. The areas of metabolic differences shown in Fig. 2 suggest that the areas of differential metabolism extend beyond the regions assessed in the primary ROI analyses. For example, greater metabolism in bilateral parahippocampal gyri extended into the hippocampus bilaterally.

4. Discussion

Our findings provide evidence of resting corticolimbic dysregulation of cerebral metabolism in euthymic older adults with bipolar disorder. Specifically, we found greater limbic and lesser cortical metabolism in bipolar patients compared to healthy controls. Our finding of corticolimbic dysregulation in euthymic older adults with bipolar disorder complements previous research that has found such differences during affective episodes in younger adults. It may be that advancing age, the accumulated damage from affective episodes, or a combination thereof, results in illness progression such that cerebral metabolism and clinical (e.g., cognitive) abnormalities encountered during affective episodes in younger adults persist between episodes in older adults (Savard et al., 1980).

In addition, our evidence of differential resting state metabolism involves regions that have been found to have metabolic or blood flow abnormalities when bipolar patients are experiencing manic or depressive episodes. For example, cerebral blood flow studies have found increased activation in the ACC and decreased activation in prefrontal cortex in manic patients while engaging in attention (Benabarre et al., 2005) or decision-making (Rubinsztein et al., 2001) tasks. In addition, SGPF (Drevets et al., 1997) and left ACC (Blumberg et al., 2000) metabolism appear to increase during mania. In healthy control subjects, the anterior cingulate cortex (ACC) has been associated with performance monitoring (MacDonald et al., 2000) and contribute importantly to motivated behavior (Mega and Cummings, 1994).

The corticolimbic dysregulation hypothesis is supported by neuroanatomical evidence of subcortical tracts between the regions involved (Schmahmann and Pandya, 2006), as well as a variety of many neuroimaging findings. Supporting evidence is largely derived from neuroimaging activation studies (usually involving a cognitive task) during depressive or manic episodes with a notable absence of studies at rest and/or during euthymia. The general rationale in activation studies is that associations between abnormal performance and particular cerebral regions in patients indicate involvement of regions implicated in the pathophysiology of bipolar disorder. While such a rationale is no doubt applicable with respect to the task studied during a given affective state, one may question the extent to which such findings generalize to euthymic states or provide information about bipolar traits, as task demands may influence regional activation differences (Strakowski et al., 2005b). Thus, methodological differences may contribute to the nature of findings. One aspect of many neuroimaging studies that may

be overlooked is that many studies use an active task (e.g., tests of memory, attention, etc.) in conjunction with neuroimaging. Our findings are noteworthy because all bipolar patients were euthymic and differences between the bipolar and control groups cannot be attributed to interactions with task demands, because the FDG-PET scans were performed at rest.

The functional significance of our findings of corticolimbic dysregulation has been detailed in other reports. For example, parahippocampal hypermetabolism and dorsolateral prefrontal hypermetabolism appear to be associated with deficits in delayed cued verbal recall in older patients (Brooks et al., 2007). Sustained attention deficits appear to be related to hypometabolism in the SGPFC and medial orbital frontal cortex as well as ventrolateral prefrontal hypometabolism (Hoblyn et al., 2007). Thus, key areas of the corticolimbic network appear to be associated with performance of important neurocognitive tasks in euthymic older adults with bipolar disorder, which highlights the clinical significance of the baseline differences reported in this paper.

Interestingly, in our sample we did not find statistically significant differences in metabolism in the SGPFC in bipolar disorder patients, as reported for younger depressed bipolar patients compared to healthy controls (Drevets et al., 1997). However, in previous work from our laboratory, subgenual prefrontal metabolism in depressed younger bipolar patients was not significantly different from that of healthy controls, despite being related to attention (Brooks et al., 2006). In the present study, however, there was a nonsignificant trend for increased left subgenual prefrontal metabolism in the bipolar group, which suggests we may not have had sufficient statistical power to detect the difference or that our rather strict definition of the SGPFC ROI was such that it did not overlap sufficiently with a region of increased metabolism in that area. It is also possible that metabolic rates in this region do not differ between euthymic older bipolar patients and healthy controls, possibly reflecting age- or mood state-related functional reorganization of corticolimbic circuits (Krüger et al., 2005).

There are several limitations of this study. First, our patients, though euthymic, were on various medications, which may have had an effect on the observed metabolic findings. However, because medications may normalize cerebral metabolism (Kennedy et al., 2001) and likely do so in varying ways, the medicated status of our patients presumably would have reduced, rather than enhanced, metabolic differences between patients and controls. A recent analysis suggested that medications may have no detectable effects in functional imaging studies of bipolar disorder (Phillips et al., 2008), although we cannot definitively rule out such effects in the current study.

Another potential limitation of our study is that we used only patients over the age of 50, which limits the generalizability of our findings to younger populations. The lack of inclusion of younger subjects in this study prevents us from drawing conclusions about interactions between age and cerebral metabolic changes in bipolar disorder, which is an important topic for future study. Although the use of a resting scan avoided the interference of the demands of an active task, the resting paradigm did not account for variations in subjects' "resting" mental processes. The limited sample size and age range of our study does not afford us the ability to evaluate reliably correlations of metabolism and illness duration across different cerebral regions. In addition, our sample size may not permit us sufficient power to detect differences in other regions, such as the ventrolateral prefrontal cortex and cerebellar vermis, which might also have been affected by the inclusion of both bipolar disorder type I and type II patients.

Nevertheless, these findings could serve as the basis for future investigations of the relations between corticolimbic dysregulation and clinical parameters in patients with bipolar disorder. Longitudinal work is necessary to explore possible interactions between age and illness

progression and the resultant effects on level of functioning. Such work is vital to understanding the deficits patients experience during both euthymia and affective episodes.

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Fig. 1.

Hypothesized corticolimbic dysregulation in bipolar disorders. Areas associated with increased activation during affective episodes in bipolar disorder are shaded red and those with decreased activation are shaded blue. Note that color-coding of regions is intended to represent the consensus findings for the region, because not all findings have been uniform. In younger adults such differences have tended to occur during mood episodes and resolve during euthymia. Numbers for Brodmann's areas are provided where appropriate. ACC = anterior cingulate cortex; AMYG = amygdala; ATC = anterior temporal cortex; CV = cerebellar vermis; DLPFC = dorsolateral prefrontal cortex; HYPH = hypothalamus; MOFC = medial orbital prefrontal

cortex; PHG = parahippocampal gyrus; SGPFC = subgenual prefrontal cortex; THAL = thalamus; VLPFC = ventrolateral prefrontal cortex.

Fig. 2.

Corticolimbic dysregulation in euthymic older adults with bipolar disorders. Axial slices with statistical parametric map of regions of relative hypermetabolism (in red) and hypometabolism (in blue) in euthymic older adults with bipolar disorders compared with healthy controls. Regions of increased and decreased metabolism are in red and blue, respectively. Talairach z (axial) coordinates are provided to the upper left of each slice.

Table 1

Demographic variables

	Bipolar <i>n</i> = 16	Control <i>n</i> = 11
Age (years)	58.7 (7.5)	58.3 (5.2)
Male/female	14/2	10/1
Education (years)	16.1 (2.8)	16.7 (3.7)
YMRS	1.6 (2.2)	0.27 (0.65)
MADRS	2.4 (3.1)	0.36 (0.81)
Months since last episode	8.7 (10.2)	—
Age at onset (years)	36.3 (15.3)	—
Illness duration (years)	22.4 (13.2)	—

Note: Standard deviations are in parentheses. YMRS = Young mania rating scale; MADRS = Montgomery–Åsberg Depression Rating Scale.

Table 2

ROI analysis of cerebral metabolism in patients with bipolar disorder compared to healthy controls

Region	<i>t</i>		Average <i>d</i>
	Left	Right	
Parahippocampal gyrus	3.83 ^a	3.71 ^a	1.45
Amygdala	2.13 ^b	3.11 ^a	1.01
Cerebellar vermis ^A	1.54 ^c		0.59
Subgenual prefrontal	1.34 ^c	-0.48	0.35
Anterior temporal	1.10	1.94 ^b	0.59
Thalamus	0.92	0.71	0.31
Hypothalamus	0.91	0.67	0.30
Medial orbitofrontal	-0.47	-0.51	0.19
Anterior cingulate	-0.94	-0.49	0.37
Ventrolateral prefrontal	-1.62 ^c	-1.59 ^c	0.62
Dorsolateral prefrontal	-2.08 ^b	-2.62 ^a	0.91

Note: Sign of *t* statistic indicates direction of difference between the groups. Thus, a positive *t* statistic indicates increased metabolism in the bipolar group relative to controls and vice versa.

^A Cerebellar vermis was considered as a whole.

^a $P < .01$.

^b $P < .05$.

^c $P < .10$.

Table 3
Regions with statistically significant differences in cerebral metabolism in bipolar disorder patients relative to healthy controls

Region	BA	Hemisphere	Talairach Coordinates			Cluster size	<i>t</i>
			<i>x</i>	<i>y</i>	<i>z</i>		
<i>Hypometabolism</i>							
Inferior and middle frontal gyri	9/45	Right	59	14	14	3179	4.88
Supramarginal gyrus/middle temporal gyrus	39/40	Right	59	-51	25	520	3.83
Middle and superior frontal gyri	6/8	Left	-24	23	39	2063	3.79
Precentral gyrus	6	Right	36	-8	57	320	3.70
Precuneus	7	Left	-2	-64	46	770	3.62
Superior and middle frontal gyrus	9	Right	18	37	35	292	3.50
Middle frontal gyrus	10	Left	-46	50	6	71	3.41
<i>Hypermetabolism</i>							
Culmen		Left	-10	-58	-6	3087	4.61
Uvula		Left	-24	-90	-22	169	4.42
Declive		Right	22	-92	-19	106	4.13
Amygdala, parahippocampal gyrus		Right	28	-9	-15	2834	4.10
Caudate		Right	32	-18	32	378	3.63
Inferior temporal gyrus		Right	20	59	-44	86	3.22

Note: Cluster size is expressed as number of voxels. For all *t*'s, *P* < .005.