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Neurochemical Abnormalities in Unmedicated Bipolar Depression and Mania: A 2D ^{1}H MRS Investigation

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Abstract

The neurobiology and neurochemistry of bipolar disorder and its different phases is poorly understood. This study investigated metabolite abnormalities in both unmedicated bipolar depression as well as mania using 2D ^{1}H Magnetic Resonance Spectroscopy Imaging (MRSI). MRSI data was obtained from 24 unmedicated Bipolar Disorder (BP) subjects (12 (hypo)manic (BPM)) and 12 depressed (BPD)), and 20 closely matched healthy controls. 2D ^{1}H MRSI data was collected from a 15 mm axial slice placed along the AC-PC line to measure brain metabolites bilaterally in the thalamus and also the anterior and posterior cingulate cortex (ACC and PCC). Brain Lac/Cr levels were significantly increased in the BP group as a whole compared to healthy controls. Glutamate abnormalities varied across bipolar state as well as brain region: significantly increased Glx/Cr values were found in the left thalamus in BPD but BPM had decreased Glu/Cr and Glx/Cr levels in the PCC when compared to healthy controls and decreased Glu/Cr levels even when compared to the BPD subjects group. The findings of the study point to state related abnormalities of oxidative and glutamate metabolism in bipolar disorder.

Keywords

MRS; bipolar disorder; mania; depression; glutamate; lactate

1. BACKGROUND

Bipolar disorder (BP) is a debilitating mood disorder with unpredictable cycles of depression (BPD) and manic episodes (BPM) interspersed with variable lengths of euthymia. The etiology of bipolar disorder is not clear though a strong biological basis is suspected due to its hereditary nature. The occurrence of the diametrically opposite mood states of mania and depression is the most striking and perplexing aspect of the illness,

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therefore, investigating the similarities and differences in the neurobiological basis of the two states is likely to increase the understanding of etiology of BP. Converging findings from animal and human studies point to the anterior cingulate-striatal-thalamic-amygdala as a putative mood regulating circuit (MRC) which may be dysfunctional in mood disorders (Anand and Charney, 2000). A number of investigators have utilized neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to investigate the pathophysiology of the MRC in BP as well as Magnetic Resonance Spectroscopy (MRS) to investigate neurochemical abnormalities within the MRC. This report focuses on MRS abnormalities in BPD and BPM.

^{1}H MRS studies have reported exciting findings regarding molecular abnormalities in BP (Strakowski et al., 2000; Moore and Galloway, 2002; Yildiz-Yesiloglu and Ankerst, 2006; Dager et al., 2008) such as decreased phosphotidyl inositol (Kim et al., 2005), decreases and increases in choline levels (Moore et al., 2000; Cecil et al., 2002; Frey et al., 2007; Michael et al., 2009; Senaratne et al., 2009), decreased or normal NAA (Winsberg et al., 2000; Brambilla et al., 2004; Dager et al., 2004; Gallelli et al., 2005; Frye et al., 2007a), elevated gray matter lactate (Dager et al., 2004; Stork and Renshaw, 2005), decreased or unchanged γ-aminobutyric acid (GABA) (Bhagwagar et al., 2007; Kaufman et al., 2009), and elevated Glx (glutamate+glutamine) concentrations (Dager et al., 2004; Michael et al., 2009; Yüksel and Öngür, 2010). ^{31}P MRS studies have reported increased phosphomonester (Kato et al., 1991; Volz et al., 1998; Yildiz et al., 2001; Silverstone et al., 2002) levels and decreased phosphocreatinine (Kato et al., 1995; Murashita et al., 2000) levels in the BPD. Decreased intracellular pH determined by ^{31}P MRS in medication-free BP patients in both the manic and depressed states and decreased frontal lobe pH are thought to indicate altered energy metabolism in BP leading to a shift towards lactic acidosis signifying abnormal brain energy metabolism which is ameliorated with lithium treatment (Kato et al., 1998; Dager et al., 2008). For a comprehensive review of MRS findings in bipolar disorder, please see Dager and colleagues (2008) and Yuksel and Ongur (2010).

Many studies conducted until present have been with medicated subjects, and though studies which include both medicated and unmedicated subjects have reported no differences between groups, the small sample size of many of these studies make it difficult to have enough statistical power to make a definitive conclusion. Furthermore, medications such as lithium have been shown to have significant effect on metabolites, such as e.g. Glx concentrations (Friedman et al., 2004). In an MRS study, Frye and colleagues found increased glutamate in medial prefrontal cortex in BPD, and lamotrigine remission was associated with decreased glutamine in the region (Frye et al., 2007b). Therefore, it is important also to study unmedicated patients. Furthermore, as different findings have been found in mania and depression a study in which subjects in both mood states are concurrently studied is required.

Most of the studies conducted at present have used a single-voxel MRS technique to study only one or several different brain regions. This procedure usually requires extended scan time. 2D MRSI has the advantage that metabolites can be measured bilaterally in homologous brain regions as well from several different brain regions within a single slice simultaneously (Brown et al., 1982). In regard to regions of interest thalamic activation and connectivity abnormalities have been reported in bipolar disorder (Anand et al., 2009) and depression (Greicius et al., 2007). The thalamus, particularly the dorsomedial nucleus, has major connections with the anterior cingulate cortex (ACC), ventral pallidostriatum, and the amygdala and is therefore central to the connections between the mood-generating limbic regions and the mood-regulating cortical regions such as the ACC and the prefrontal cortex (Taber et al., 2004; Garakani et al., 2007). Thalamic lesions have been associated with both mania and depression (Cummings, 1995). Furthermore, neurochemical abnormalities such

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as increased monoamine producing neurons (Zubieta et al., 2000) and increased NAA have been reported in the thalamus in bipolar disorder (Zubieta et al., 2000; Deicken et al., 2001). Therefore, in this study, we investigated primarily thalamic MRS metabolite abnormalities in bipolar disorder.

Using 2D MRSI we chose an appropriate slice to include the thalamus. In using the 2MRSI slice approach we were also able to sample metabolites from the rostral anterior cingulate cortex (ACC) and the posterior cingulate cortex (PCC). ACC is also of particular interest in mood disorders as it is a brain region which is intimately involved in mood regulation (mainly its ventral area) (Critchley et al., 2003) as well as in conflict resolution (Etkin et al., 2006), while responding to emotional stimuli. The ACC also has significant connections with the thalamus. The PCC has recently been identified as a major hub of the brain's default mode circuit involved in non-task based attention and readiness of response to external and internal environment (Raichle et al., 2001). Abnormalities of attention to both external and internal environment are frequently seen in BPM and BPD in terms of distractability and excessive rumination respectively.

In summary, a number of disparate metabolite abnormalities have been reported in bipolar disorder. However, many of these findings have not been replicated or opposite findings reported in different studies. The lack of characterization of phase of the disorder, medication status of patients, or of the anatomical area from which measurements were taken have made it difficult to interpret the findings of some of these studies in terms of the pathophysiology of bipolar disorder.

Therefore, in this study, we investigated neurochemical differences primarily in the thalamus but also the ACC and PCC, concurrently, in unmedicated BPD and BPM, as well as in matched healthy controls, using a single slice 2D ^{1}H MRSI technique with short echo time. This technique allows us to detect several commonly measured metabolite levels, such as N-acetylaspartate (NAA), Creatine (Cre), tCho (choline-containing compounds), and myoinositol (mI) as well as Lactate (Lac), Glutamate (Glu), and Glx) in order to investigate the subtle changes of brain chemistry related to different stages of bipolar patients (Brambilla et al., 2005). Based on the literature reviewed above, we hypothesized that abnormalities of metabolites in the brain and in particular the thalamus will be present in BPD and BPM when compared to healthy controls and that some of these abnormalities would be similar in both groups (possibly signifying trait related changes) while others would be in opposite directions signifying specific state related changes.

2. METHOD

2a. Subjects

Medication free bipolar depressed (BPD) (N = 12, Age: 37 ± 10 yrs; 6F) and bipolar manic (BPM) (N = 12, Age: 31. ± 13 yrs, 9F) outpatients were recruited from the outpatient clinic at University Hospital, Indiana University School of Medicine and by advertisement from the community. Healthy controls matched for age and gender (N = 20, Age: 31 ± 9yrs; 13F) were recruited via advertisement. All subjects took part in the study after signing an informed consent form approved by the Investigational Review Board (IRB) at Indiana University School of Medicine. Both patients and healthy control subjects were paid $75 for screening and $75 for the MRI scan. All subjects underwent a detailed structured diagnostic interview, the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) and or the Mini-International Neuropsychiatric International Interview (MINI) (Sheehan et al., 1998), which generated a DSM-IV diagnosis. To be included in the study, BP patients had to satisfy DSM-IV criteria for Bipolar Disorder either in the hypomanic or manic state (Young Mania rating Scale (Young et al., 1978) (YMRS) > 12; 17-item Hamilton

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Depression Rating Scale (Hamilton, 1976) HDRS < 18) or in the depressed state (HDRS > 15; YMRS < 12). Exclusion criteria for patients were: meeting DSM-IV criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, atypical psychosis, anxiety disorder as a primary diagnosis, mental retardation or meeting full criteria for personality disorder; history of receiving electroconvulsive therapy in the past year; use of psychotropics in the past 2 weeks; use of fluoxetine in the past 5 weeks; use of lithium in the past 6 months; acutely suicidal or homicidal or requiring inpatient treatment; meeting DSM-IV criteria for substance dependence within the past 6 months or abuse within the past 3 months, except caffeine or nicotine; positive urinary toxicology screening at baseline; use of alcohol in the past 1 week; serious medical or neurological illness; current pregnancy or breast feeding; metallic implants or other contraindications to MRI. Inclusion criteria for healthy subjects were: ages 18–60 years and ability to give voluntary informed consent; no history of psychiatric illness or substance abuse or dependence; no significant family history of psychiatric or neurological illness; not currently taking any prescription or centrally acting medications; no use of alcohol in the past 1 week; and no serious medical or neurological illness. Exclusion criteria for healthy subjects were: under 18 years of age; pregnant or breast-feeding; metallic implants or other contraindication to MRI.

2b. Behavioral Ratings

Subjects were rated on the 17-item Hamilton HDRS and the YMRS at the time of the baseline scan.

2c. MRI/MRSI scans

All subjects underwent a 2D MR spectroscopic imaging (MRSI) exam of the brain as well as a structural MRI scan. All participants gave written informed consent prior to scans. ^{1}H MRSI acquisitions and related brain imaging were conducted on a 3T Tim Trio (Siemens Healthcare) MR scanner equipped with a standard 12-channel head coil array. A 15mm axial slice was placed along the AC-PC line in a way to cover anterior cingulate cortex (ACC), thalamus as well as posterior cingulate cortex (PCC) (Fig. 1). Spectroscopic data were acquired from this slice with a nominal voxel size of 2.8 ml (13.75 × 13.75 × 15 mm^3), TR/TE = 1500ms/30ms and 4 repetitions were obtained in approximately 7 minutes.

2d. MRS data processing and analysis

All MRS processing was carried out blinded to diagnosis and a single MRSI voxel was manually chosen from each subject's T2-weighted image to represent each of the following brain areas: left ACC, right ACC left thalamus, right thalamus, and left and right PCC (Figure 1). All the ROIs were located in gray matter areas. Typical voxels chosen from these areas were quantified using the spectral-fitting package LCModel (version 6.2) (Provencher, 1993) as shown in Figure 2. The fitting results are given as ratio to total creatine (Cr). Only spectra with Full Width at Half Maximum (FWHM) < 0.15 ppm, signal-to-noise ratio (SNR) > 10 and metabolite concentration fitting results with Cramér–Rao lower bound (CRLB) ≤ 30% were used for statistical analysis. While the error of the Gln fits was too large to pass inclusion criteria, the Glu and combined signal of Glu+Gln (Glx) were fitted with CRLB ≤ 30% in many cases and could thus be reported. Results for left and right ACC were then averaged to correspond to one ROI for ACC (covering left and right ACC) and one ROI for PCC (covering left and right PCC). This was done because, for midline structures, enough resolution is not present to report lateralized results.

2e. Statistical analysis

R-2.13.2 (www.r-project.org) was used to perform the statistical analyses. Demographic variables (age and gender) and clinical variables (YMRS and HDRS) were compared among

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the 2 BP groups and the control group using the Mann-Whitney test for the continuous variables and the Fisher's exact test for the categorical variables (Table 1). An exploratory analysis was used to examine the distribution of the metabolites in each group. Metabolite concentrations away from the median by more than 3.5 times the median absolute deviation were considered to be outliers and excluded from further analysis.

Out of the all the metabolites fitted by LCModel, a total of 7 commonly measured metabolites passed the above criteria of giving fitting results with CRLB ≤ 30% and were thus used in the statistical analysis. We followed a common practice of analyzing the relative metabolite concentrations expressed as their ratios over the Creatine (Cr) level. Such analysis is only valid when the Cr levels are stable across the diagnosis groups and brain regions. Linear mixed models with the diagnosis groups, brain regions and their interaction as predictors and subjects as a grouping variable were used to study the Cr stability.

The metabolite concentration ratios over Creatine (Cr) were analyzed using linear mixed models - LMM (43) with the diagnosis and the brain region as the independent covariates adjusted for subjects' age and gender. The models take into account the correlations between the metabolite ratios obtained from the same patient in different brain regions. LMMs have a big advantage over the repeated measures ANOVA, since they can deal with missing observations within subjects. That is, it is not necessary for all the metabolite measurements in all brain regions to pass the criteria for inclusion into the analysis for the patient to be included in the analysis. After the quality control was applied in the MRS processing step, N=174 spectra from 44 subjects were used in the statistical analyses with 82 spectra available in the thalamus, 44 spectra in ACC and 48 in PCC. Notably, there were no differences detected in the missingness patterns between the BPM, BPD and HC groups as determined by the logistic regression analyses (results not reported).

The main effects of the diagnosis (BPD, BPM, and controls), brain region (ACC, right thalamus, left thalamus, and PCC) and their interaction, adjusted for possible confounders (age and gender), were analyzed using LMMs as our primary statistical analysis tool. First, the interaction effect of diagnosis by brain region was tested to see whether differences observed among diagnosis groups (BPD, BPM, and HC) are brain region specific. If the test for interaction effect was not significant at $\alpha = 0.05$ level, the main effects only model was fit and reported, assuming that the reported metabolic change was not brain region specific. To investigate common abnormalities in both phases of the disorder, the same analysis strategy was repeated to examine the differences between the BP group as a whole (combined BPD and BPM) and the healthy controls. When the hypotheses of no interaction or diagnosis effects were rejected in the primary analysis, post-hoc pairwise tests for the metabolite differences between the diagnosis groups were performed. Keeping in mind that this was a proof of concept study, we report the p-values unadjusted for multiple comparisons and discuss the findings taking into account the possibility of false positive findings.

Finally, the correlation between metabolite levels and clinical variables were explored using Pearson correlation coefficient.

3. RESULTS

No differences were found between the 3 groups by either age ($p = 0.25$) or gender ($p = 0.45$). As expected, YMRS was significantly higher in the BPM group when compared to the BPD patients ($p < 0.001$), while HDRS was significantly higher in the BPD group when compared to the BPM group ($p < 0.001$) (Table 1).

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Examination of the Cr levels by diagnosis group and brain regions showed that we have no evidence in our data to reject the Cr level stability hypothesis. No differences in the Cr levels were found by the diagnosis groups ($F(2, 41) = 0.11$, $p = 0.90$), brain regions ($F(3, 87) = 0.97$, $p = 0.41$) or their interaction ($F(6, 87) = 0.91$, $p = 0.49$).

Results of the analyses comparing the metabolite levels as a function of the diagnosis and brain region are summarized in Table 2.

3a. Interaction effect of diagnosis by brain region

In the 3-group (BPM, BPD and HC) analysis, an interaction effect of the diagnosis by the brain region was found for the Glx/Cr level ($F(6, 79) = 2.54$; $p = 0.03$) and for the Glu/Cr level ($F(6,76) = 2.99$; $p=0.011$).

Post-hoc pair-wise comparison analysis showed that when compared to the HC group: (1) BPM group had lower Glx/Cr levels in the PCC ($p = 0.013$) and (2) the BPD group had higher Glx/Cr levels in the left Thalamus ($p=0.023$).

The BPM group showed significantly decreased Glu/Cr levels in the PCC when compared to the HC group ($p = 0.0002$) and when compared to the BPD group ($p=0.022$).

In the 2-group comparison (figure 4), diagnosis and brain region interaction was significant for the Glx/Cr level $F(3, 82) = 4.54$; $p = 0.005$) and Glu/Cr level ($F(3, 79) = 4.50$; $p=0.006$). Post-hoc tests revealed that the BP group had lower Glx/Cr levels in the PCC ($p = 0.036$) when compared to the HC group and lower Glu/Cr levels in the PCC ($p = 0.004$).

3b. Main Effect of Diagnosis

In the 3-group comparisons, there were no statistically significant diagnosis effects for any metabolites considered.

Diagnosis was a significant factor in the 2-group comparison for the Lac/Cr levels ($F(1,40) = 4.99$, $p = 0.03$). BP group had higher overall Lac/Cr levels compared to the HC group (Figure 4).

3c. Main Effect of Region

In both, 3- and 2-diagnosis-group comparisons, significant differences were found between the Lac/Cr, mI/Cr, tCho/Cr and NAA/Cr levels across different brain regions (Table 2). These regional differences are expected and have also been reported in other studies (Yüksel and Öngür, 2010).

3d. Correlation with depression and mania scores

None of the correlations between metabolites levels and HAM-D and YMRS scores were found to be significant either in the BP group as a whole or within the subgroups.

4. DISCUSSION

The results of this study show a significantly increased Lac/Cr in the BP group as a whole regardless of region. Lactate is important in brain bioenergetics and can be increased in states of brain injury, hypoxia or increased metabolism which are accompanied with a redox shift towards anaerobic metabolism (Dager et al., 2008). As reviewed in the introduction, a number of studies point to abnormalities of the brain energy metabolism in BP disorder. Decreased frontal lobe pH observed in BP patients has been attributed to lactic acidosis (Kato et al., 1998; Dager et al., 2008). A previous study in unmedicated BP subjects also

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reported increased Lac in gray matter in an axial section centered around the anterior cingulate (Dager et al., 2004). The abnormalities of a general increased Lac/Cr in the brain and in the thalamus indicate impairment in the normal brain-energy metabolism in the BP group, particularly in BPM.

On the other hand, in this study, abnormalities of Glx/Cr and Glu/Cr seem to be state related and also different in different brain regions. In the thalamus, increased Glx/Cr levels were found in BPD while these abnormalities were not seen in the ACC and PCC regions. The observation of increased levels of Glx levels is congruent with other reports which have reported increased glutamate metabolism in bipolar disorder as reviewed in the introduction section (Dager et al., 2004; Michael et al., 2009; Yüksel and Öngür, 2010). However, in BPM decreased Glx/Cr and Glu/Cr levels were seen in the PCC region compared to healthy subjects and decreased Glu/Cr levels were seen even compared to the BPD subjects. That both Glu and Glx were decreased suggests that a primary abnormality in glutamate metabolism is present in the PCC region in mania. The decreased levels of glutamate in mania is different from previous studies though no previous study has directly measured glutamate in the PCC in unmedicated mania. The interpretation of this finding is difficult and can only be speculated upon at this time. However, as reviewed above, the PCC area has received much attention recently as a central node of the so call default mode circuit of the brain. The default mode circuit has been implicated in the task-free brain state of vigilance regarding the external environment as well as rumination about inner mental processes (Raichle et al., 2001). An abnormality in the PCC may signify an abnormality in this circuit which could disrupt these mental processes leading to distractability as well as decreased attention to internal mental processes frequently seen in mania.

Furthermore, increased glutamate transmission induced toxicity is an attractive hypothesis that has been proposed for the pathophysiology and for developing treatments for many neuropsychiatric disorders disorders (Krystal et al., 1999). However, until present a definitive glutamate abnormality has not been found in any psychiatric disorder including schizophrenia. Recently, there has been much interest in the observation that glutamatergic antagonists have antidepressant properties (Berman et al., 2000). Therefore the low Glx and Glu seen in mania and an increase Glx seen in BPD can be interpreted in that context. However, MRS is unable to distinguish between intracellular glutamate and extracelluar glutamate transmission and the relationship of these findings to particular mood states can only be speculated upon at this time.

This report concurrently compare distinct groups of unmedicated BPD and BPM subjects. Strict quality criteria for inclusion of spectroscopic data and fitting results were used, which on one side decreased the sample size, yet on the other hand ensured proper technical results. The sample size of our study was relatively large for a study of unmedicated BP subjects, a group which is difficult to recruit and study in the unmedicated state. However, the sample size was not large enough that we could correct for multiple comparisons for the number of metabolites or the number of ROIs studied. Correction for all multiple comparisons would require a very large number of subjects, which is difficult in this hard-to-study population. It should be noted that we expect to find approximately 1 association by chance to be significant at 0.05 level when making 18 comparisons. However, in our study we found 5 significant differences, which have a very small probability of happening by chance only.

Though the findings of this study are not confounded by concurrent use of medication, long-term effects of past use of medications cannot be fully ruled out. To fully account for medication effects, drug-naïve patients would have to be studied which is a difficult proposition particularly for the recruitment of bipolar patients. Finally, to investigate truly

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trait related abnormalities in bipolar disorder, this investigation will also have to be conducted in euthymic subjects in future studies.

In summary, the findings of this study point to abnormalities of oxidative and glutamate metabolism in BP and in particular in BPM. Further studies in a larger number of subjects are needed to confirm the findings of this study.

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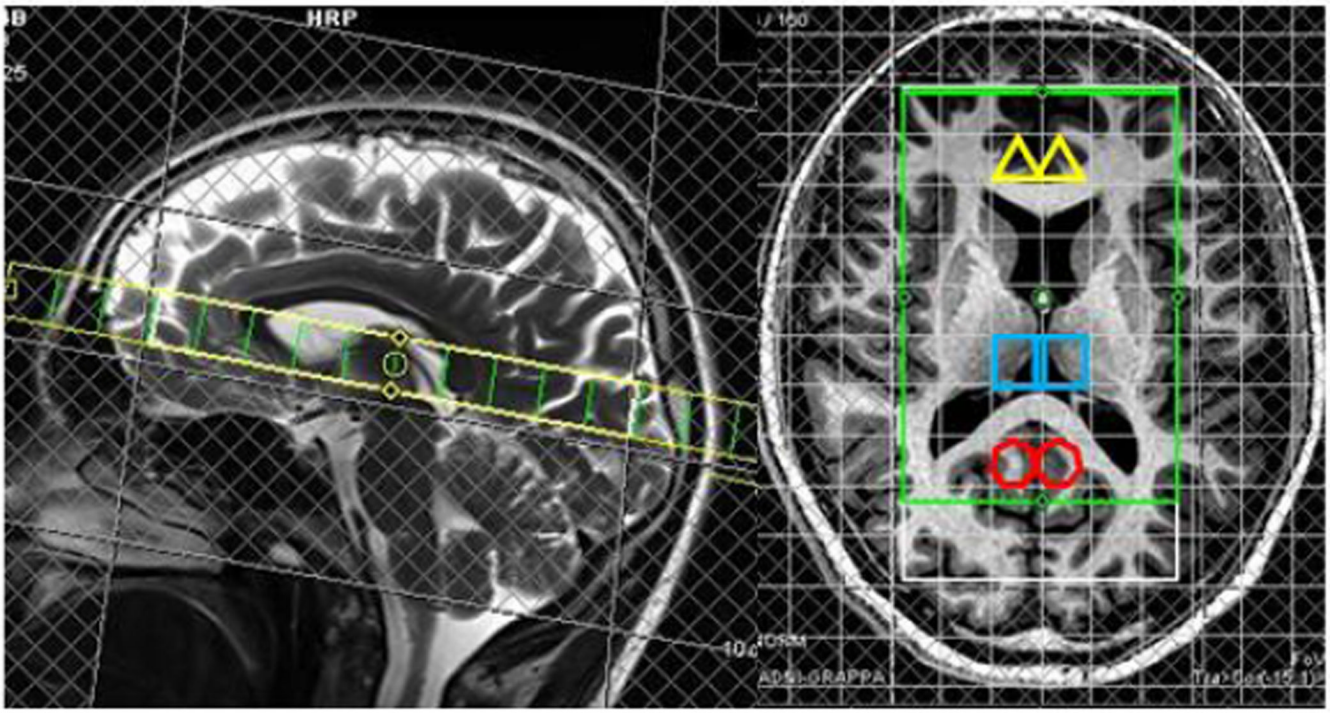

Figure 1.
Representative placement of the MRSI slice on a T2-weighted sagittal image (left). Typical voxel selection for the region of interest analysis is illustrated on the same subjects' T1-weighted image (right). ACC, thalamus and PCC are indicated by triangles, squares and circles, respectively.

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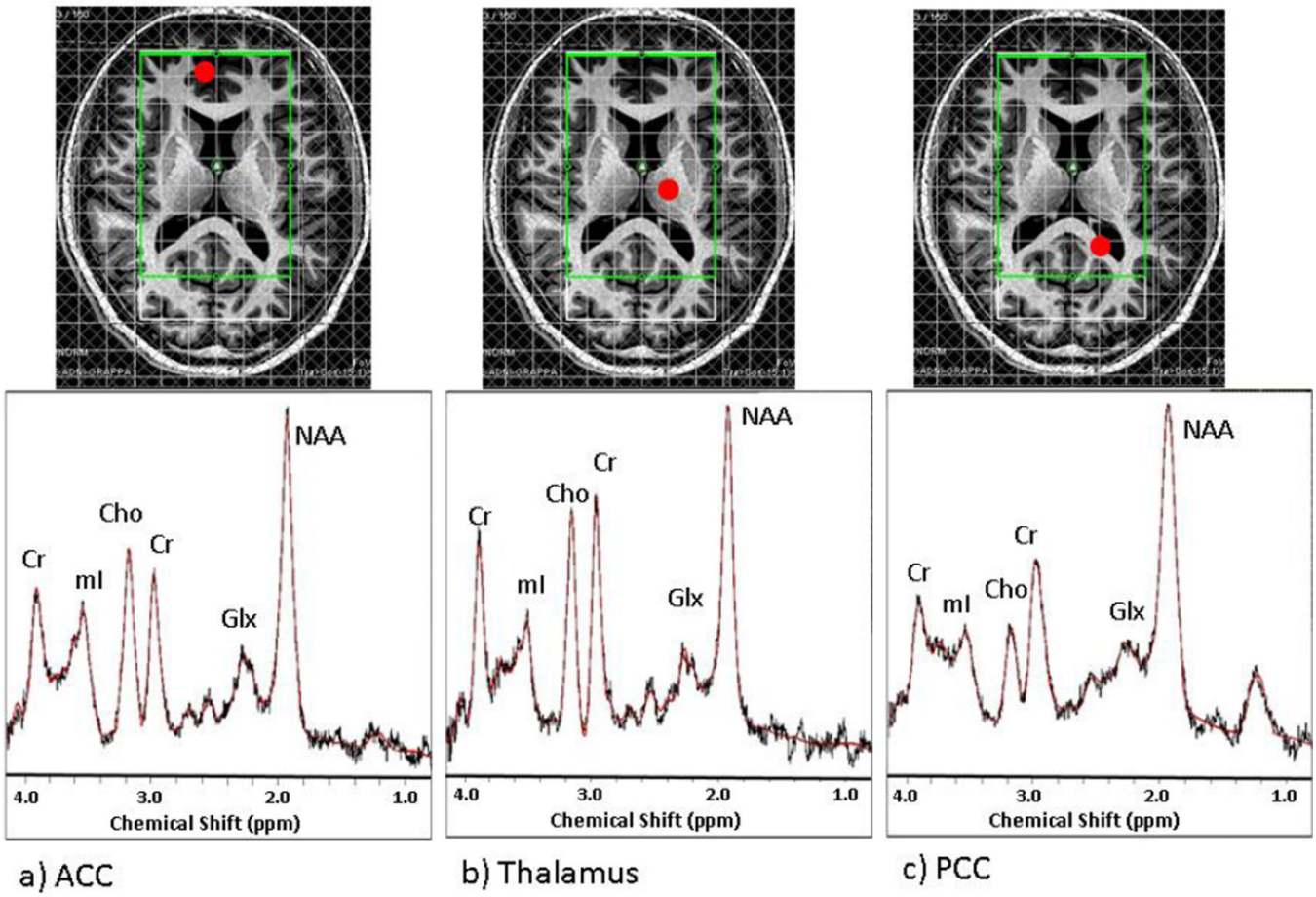

Figure 2.
Representative MR spectrums from Regions of Interests. Raw data and LC Model spe in thick black and fine red lines respectively.

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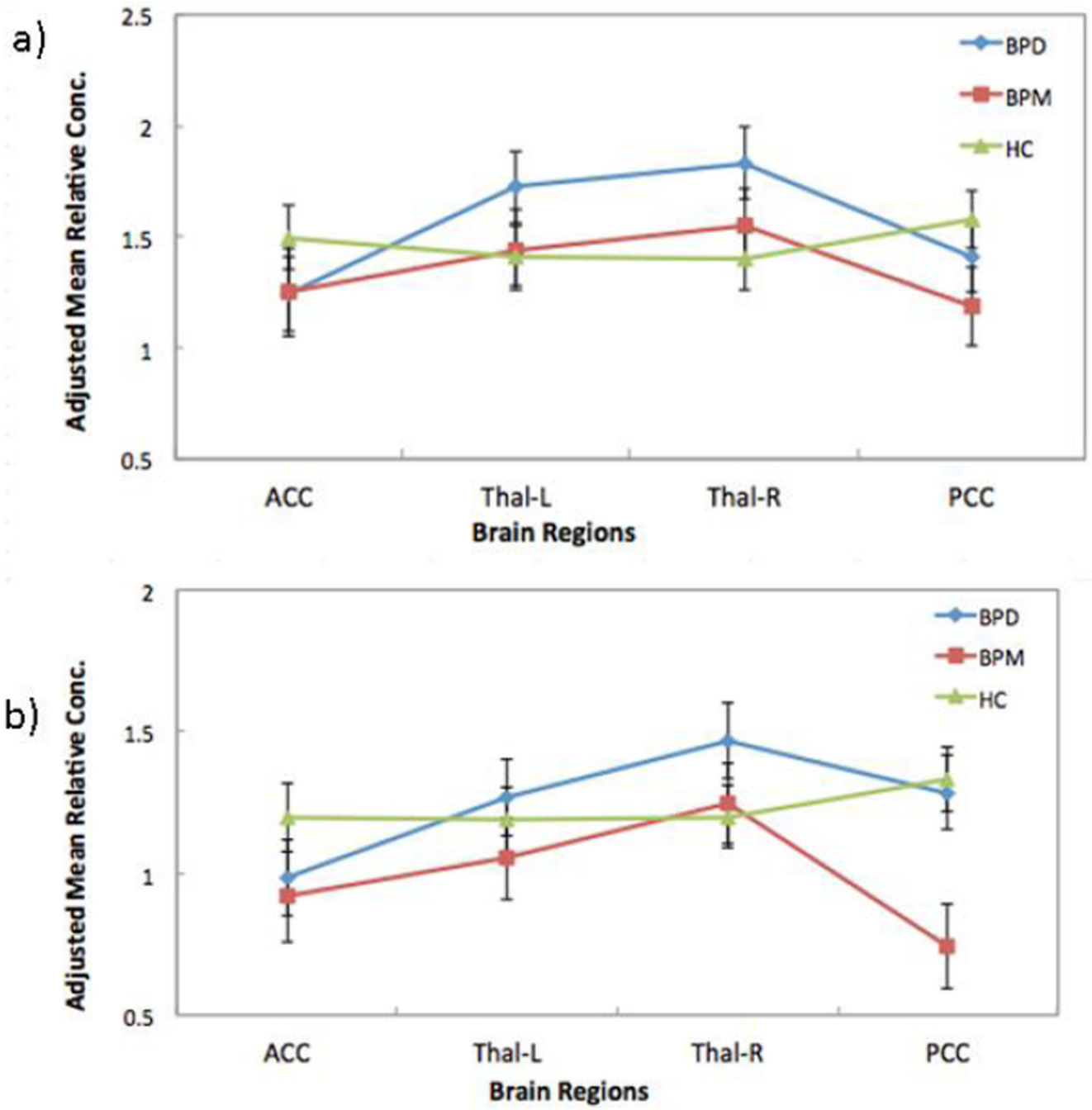

Figure 3.

Diagnosis by brain region interaction effect on (a) Glx/Cr and (b) Glu/Cr levels for 3-group comparison represented as mean ± SE values adjusted for age and gender. BPD: Bipolar Depression; BPM: Bipolar Mania; HC: Health Controls. ACC: Anterior Cingulate Cortex; Thal-L: Thalamus Left; Thal-R: Thalamus Right; PCC: Posterior Cingulate Cortex.

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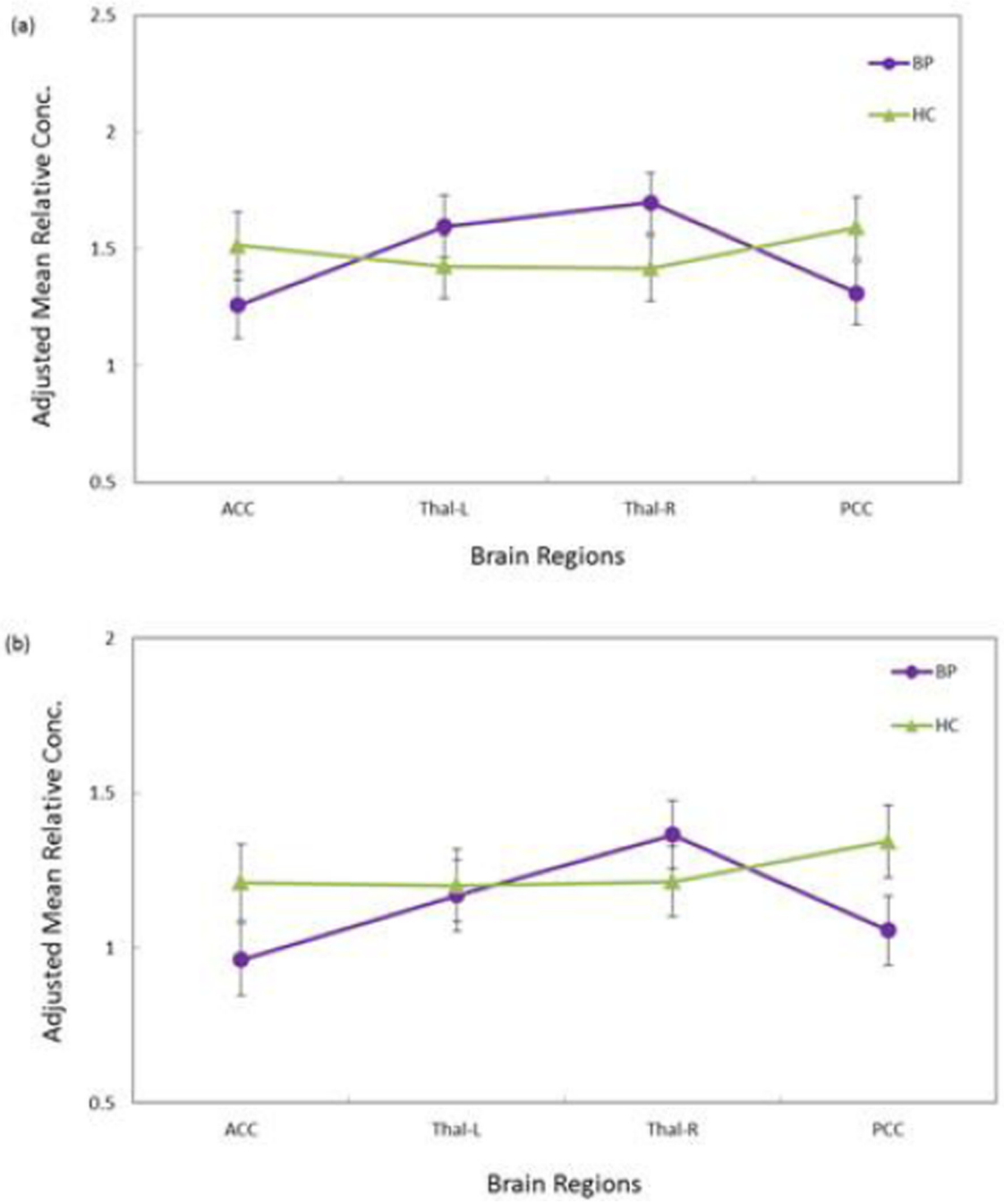

Figure 4.
Diagnosis by brain region interaction effect on Glx/Cr (a) and Glu/Cr (b) levels for 2-groups comparison represented as mean ± SE values adjusted for age and gender.

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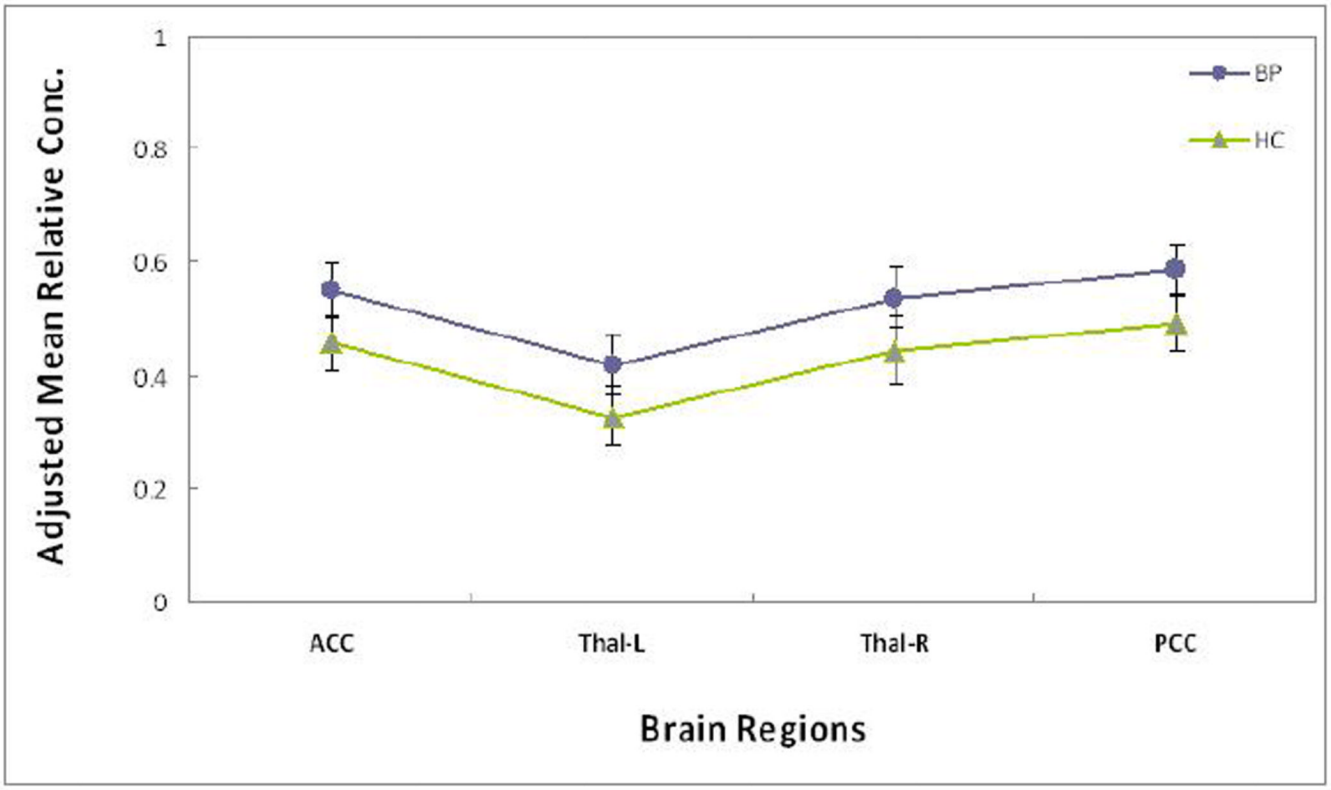

Figure 5.

Lac/Cr levels for 2-group comparison represented as mean ± SE values adjusted for age and gender. BP: Bipolar Disorder; HC: Health Controls. ACC: Anterior Cingulate Cortex; Thal-L: Thalamus Left; Thal-R: Thalamus Right; PCC: Posterior Cingulate Cortex.

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TABLE I

Clinical and demographic information by group. BPD: Bipolar Depressed; BPM: Manic; HC: Healthy Controls.

Measure	BPD (N=12) Mean (SD)	BPM (N=12) Mean (SD)	HC (N=20) Mean (SD)	p-value (ANOVA)
Age (years)	37 (10)	31 (13)	31 (9)	0.247
Age at first episode (years)	13 (4)	12 (4)		0.501
Hamilton Depression Rating Scale score (17 item)	19 (3)	7 (4)		< 0.001
Young Mania Rating Scale score	3 (3)	17 (2)		< 0.001
	Median (Range)	Median (Range)		p-value (Mann-Whitney)
Period off medication prior to scan (months)	6 (1 – 108) Drug naïve: 3	36 (4 – 120) Drug naïve: 1		0.110
Number of prior mood episodes (depression)	15 (4–123)	16 (3–102)		0.668
Number of prior mood episodes (mania)	22 (2–310)	121 (4–447)		0.308
Time since last manic episode (months)	4 (1–19)	5 (1–60)		0.578
Time since last depressive episode (months)	6 (1–21)	3 (1–48)		0.087
Duration of current episode (weeks)	4 (2–28)	1.5 (.7–8)		0.002
	N (%)	N (%)	N (%)	p-value (Fisher exact)
Female	6 (50%)	9 (75%)	13 (65%)	0.620
Caucasian	10 (83%)	12 (100%)	18 (90%)	0.364
Trauma history	4 (33%)	8 (67%)		0.220
History of suicide attempt	4 (33%)	8 (67%)		0.220
History of psychosis	2 (17%)	2 (17%)		1.000
Bipolar I	5 (42%)	6 (50%)		1.000
Bipolar II	7 (58%)	6 (50%)		
History of alcohol abuse	7 (58%)	3 (25%)		0.214
History of drug abuse	6 (50%)	6 (50%)		1.000

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Table 2

Effects of the diagnosis (3 groups: BPD, BPM, HC; and 2 Groups (BP and HC), brain regions and their interactions on the metabolite levels based on the linear mixed models adjusting for subjects' age and gender as well as within-subject correlations. When the interactions were not significant, the results of the main effects only model are presented. BPD: Bipolar Depressed; BPM: Manic; BP: Bipolar; HC: Healthy Controls. NAA: N-acetylaspartate, Cre: Creatine, tCho: choline-containing compounds, and ml: myoinositol, Lac: Lactate, Glu: Glutamate, and Glx: Glutamate+Glutamine.

	Diagnosis	**Brain regions**	**Brain region × Diagnosis**
Lac/Cr (3 groups)	$F(2,39) = 2.61$, $p = 0.09$	$F(3,54) = 3.48$, $p = 0.02$	$F(6,48) = 1.53$, $p = 0.19$
(2 groups)	$F(1,40) = 4.99$, $\mathbf{p = 0.03}$	$F(3,54) = 3.51$, $p = 0.02$	$F(3,51) = 0.88$, $p = 0.46$
Glx/Cr (3 groups)	*Interaction*	*Interaction*	$F(6,79) = 2.54$, $\mathbf{p = 0.03}$
(2 groups)	*Interaction*	*Interaction*	$F(3,82) = 4.54$, $\mathbf{p = 0.005}$
mI/Cr (3 groups)	$F(2,40) = 0.58$, $p = 0.57$	$F(3,91) = 6.60$, $p < 0.001$	$F(6,85) = 0.98$, $p = 0.44$
(2 groups)	$F(1,41) = 0.67$, $p = 0.42$	$F(3,91) = 6.66$, $p < 0.001$	$F(3,88) = 1.84$, $p = 0.15$
tCho/Cr (3 groups)	$F(2,40) = 0.96$, $p = 0.39$	$F(3,92) = 24.56$, $p < .0001$	$F(6,86) = 1.10$, $p = 0.66$
(2 groups)	$F(1,41) = 0.40$, $p = 0.53$	$F(3,92) = 24.55$, $p < .0001$	$F(3,89) = 1.09$, $p = 0.07$
NAA/Cr(3 groups)	$F(2,40) = 1.31$, $p = 0.28$	$F(3,90) = 5.05$, $p = 0.003$	$F(6,84) = 0.70$, $p = 0.65$
(2 groups)	$F(1,41) = 2.41$, $p = 0.13$	$F(3,90) = 5.07$, $p = 0.003$	$F(3,87) = 0.82$, $p = 0.49$
Glu/Cr (3 groups)	*Interaction*	*Interaction*	$\mathbf{F(6,76) = 2.99, p = 0.011}$
(2 groups)	*Interaction*	*Interaction*	$\mathbf{F(3,79) = 4.50, p = 0.006}$