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A longitudinal pilot proton MRS investigation of the manic and euthymic states of bipolar disorder

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Several lines of evidence implicate dysfunction in brain energy production as a key component of bipolar disorder. In particular, elevated brain lactate levels observed in this condition suggest a shift from aerobic to anaerobic metabolism, possibly as a result of mitochondrial abnormalities. Most prior imaging studies of brain metabolites were performed in either euthymic or depressed bipolar patients or compared different populations in different mood states. We sought to measure brain metabolite concentrations in the same patients in both manic and euthymic states. Given the dramatic changes in clinical state of bipolar disorder patients, we hypothesized that previously observed abnormalities in lactate concentrations in bipolar disorder might show state dependent changes. In this study 15 patients (mean age 36.1 years) diagnosed with bipolar I disorder underwent proton magnetic resonance spectroscopy of the anterior cingulate cortex and parieto-occipital cortex during hospitalization for acute mania (mean Young Mania Rating Scale (YMRS) 22.1). Seven of these subjects returned (mean interval 21.16 months) to have imaging repeated while euthymic (mean YMRS 2.0). A group of age- and gender-matched control participants (N = 6) were scanned as well. We report that during mania, bipolar disorder subjects had lactate levels comparable to healthy control subjects but during euthymia these levels were significantly reduced. No significant change was observed for other metabolites. These results implicate mood dependent alterations in energy metabolism in the biology of bipolar disorder. Additionally, this finding has potential use as a biomarker for both evaluating novel treatments as well as diagnostic clarification between mood disorders.

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Introduction

Multiple lines of evidence suggest that metabolic dysfunction is a key feature of bipolar disorder (see Stork and Renshaw1 and Dager et al.2 for review). In particular, disease-specific abnormalities of mitochondria and energy production have been observed in bipolar disorder.3–6 Although these investigations have accumulated evidence linking metabolic dysfunction to the bipolar disorder trait, the role of metabolic dysfunction in switches between clinical states of depression, mania and euthymia has never been well characterized.

Prior studies have compared different mood states in separate populations of patients with a bipolar disorder diagnosis. These cross-sectional studies use a design, which compares populations whose clinical and treatment histories and prognosis vary widely. Prior longitudinal studies demonstrated that patients who present with mania and receive a bipolar disorder diagnosis will have variable clinical courses with different levels of inter-episode impairment, widely varying temporal courses and possibly very different eventual diagnoses.6,7 Clearly, a longitudinal study design with intra-subject measures of the same patients in different mood states would allow better characterization of state related physiological changes.

Few prior studies of brain metabolism in bipolar disorder have utilized high field magnetic resonance spectroscopy (MRS), which allows improved characterization of in vivo neurochemistry over older techniques. In this 4T Proton MRS study, we measured brain metabolite concentrations, including lactate, a measure related to energy metabolism, in the anterior cingulate cortex (ACC) and parietal occipital cortex (POC) in a cohort of medicated patients with a diagnosis of bipolar disorder type I. We chose the ACC because it is a region strongly implicated in the pathophysiology of bipolar disorder.8 We chose the POC as the comparison region. To increase the power of our study and minimize medication confounds, we performed our assessments in a single cohort of patients when they were clinically manic and in the same patients when they were clinically euthymic. An age and gender matched set of healthy control (HC) subjects were also scanned using the same protocol. We hypothesized that given the dramatic changes in clinical state of bipolar disorder patients, abnormalities in markers of brain metabolism previously observed in bipolar disorder might show state dependent changes.

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Materials and methods

Subjects. Subject recruitment and proton MRS imaging were performed at the McLean Hospital, (Belmont, MA, USA) as previously described. Following approval by the Institutional Review Board of McLean Hospital, 39 subjects diagnosed with bipolar I disorder in a current manic state as per DSM-IV were recruited from a psychiatric inpatient unit. Twenty-two HC subjects were recruited concurrently. Diagnoses were determined by consensus based on structured clinical interviews for DSM disorders by a trained clinician, and all available clinical data. Subjects with significant neurological or medical problems, current substance abuse, or history of substance dependence were excluded. Tobacco smokers were not excluded from the study. All patients had negative urine toxicology tests at the time of scanning. Patients were assessed using the Young Mania Rating Scale (YMRS), Positive And Negative Syndrome Scale (PANSS) and Montgomery-Asberg depression rating scale (MADRS) on scan days. Current medication regimens were recorded and chlorpromazine (CPZ) equivalents were calculated for patients taking antipsychotic medications. HC subjects were assessed using the structured clinical interviews for DSM disorders to rule out axis I disorders. None of the patients met criteria for rapid cycling. Usable data were obtained from 21 HC and 15 BD subjects. Twenty-two patients were unable to tolerate the scanning environment because of their psychiatric condition and were therefore not included in the study. Two other patients elected to enter the study but refused the scan after structured clinical interviews for DSM disorders and symptoms scales were collected. The bipolar I disorder subjects who did not complete the study were more symptomatic than those who completed the study (non-completer average YMRS: 26.9; MADRS: 18.4; PANSS: 82.0; completer average YMRS: 24.7, MADRS: 11.1, PANSS: 59.6). Patients with bipolar disorder in a manic phase who completed the 4T MRS scan and symptom scales were subsequently contacted (between 12–50 months later) for follow-up assessments. These patients were re-assessed with the same exclusion criteria described above. At follow-up, all were clinically euthymic and none met DSM-IV criteria for mania, hypomania or major depressive episode. Although symptomatology score cutoffs were not used to define euthymia for the purposes of inclusion, the scores recorded at the time of the second scan suggest subjects were no more than minimally symptomatic (Table 1). Eight subjects were successfully contacted, met criteria for inclusion and consented for the study. Seven subjects were able to complete the follow-up scan and repeat symptomatology scales. Compared with subjects that successfully completed the follow-up study, subjects that completed the first scan but were unable to complete the follow-up study did not differ significantly in their distribution of symptoms at the time of the first scan: Completer YMRS: 22.1 ± 8.2 versus non-completer YMRS: 27 ± 9.3 (P = 0.31), completer MADRS: 12.7 ± 3 versus non-completer MADRS: 9.6 ± 3.6 (P = 0.095), completer PANSS: 56.3 ± 13 versus non-completer PANSS: 62.5 ± 14.9 (P = 0.41).

Among the bipolar subjects that completed both manic and euthymic scans, no patients met DSM-IV criteria for panic disorder, a diagnosis with known trait differences in brain lactate responsivity to chemical challenges. Two subjects met DSM-IV criteria for prior diagnosis of EtOH abuse. In neither case did the subject meet criteria within the 5 years before entering the study and neither engaged in daily EtOH use at any point. One of these two subjects also endorsed cannabis use that met DSM criteria for abuse over a period of 2 weeks a decade before entering the study. No other subjects described substance use that met criteria for abuse or dependence at any point currently or historically.

Magnetic resonance imaging/MRS scans. Proton MRS acquisitions were conducted on a 4 Tesla full body magnetic resonance scanner (Varian/UnityInova, Varian, Palo Alto, CA, USA), using a 16-rung, single-tuned, volumetric birdcage coil (Robarts Research Institute, London, Ontario, Canada). Two-dimensional (2-D) gradient-recalled echo images (12 s) were acquired in three planes to ensure optimal patient scanning. Patients were assessed using the Young Mania Syndrome Scale; SGA, second generation antipsychotic, YMRS, Young Mania Rating Scale. Abbreviations: CPZ, chlorpromazine; F, female; M, male; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SGA, second generation antipsychotic, YMRS, Young Mania Rating Scale. Mean ± s.d. where appropriate.

Numbers in medication rows are the number of subjects whose regimen includes that class of psychotropic medication. In addition to psychotropic medications, three bipolar subjects were prescribed other medications including one patient taking anti-hypertensive medication, one subject taking a statin, anti-hypertensive medication and oral anti-hyperglycemic medication and one subject taking a statin and a oral anti-hyperglycemic medication.

Table 1 Subject demographics and clinical information

|                  | Healthy control (N = 6) | Bipolar manic (N = 7) | Bipolar euthymic (N = 7) |
|------------------|-------------------------|-----------------------|--------------------------|
| Age              | 35.2 ± 8.1              | 37.6 ± 10.7           | 39.7 ± 10.9              |
| Gender           | 3 M, 3 F                | 3 M, 4 F              | 3 M, 4 F                 |
| MADRS            | 12.7 ± 2.9              | 3.7 ± 2.7             | 2.0 ± 3.2                |
| YMRS             | 22.1 ± 8.2              | 2.0 ± 3.2             | 2.7 ± 3.0                |
| PANSS            | 56.3 ± 13.0             | 35.4 ± 3.7            |                         |
| Anticonvulsants  | 5                       | 3                     |                         |
| SGAs             | 7                       | 5                     |                         |
| Lithium          | 4                       | 5                     |                         |
| CPZ equivalents  | 343 ± 154               | 352.2 ± 437           |                         |
| Benzodiazepines  | 5                       | 2                     |                         |

Abbreviations: CPZ, chlorpromazine; F, female; M, male; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SGA, second generation antipsychotic, YMRS, Young Mania Rating Scale, Mean ± s.d. where appropriate.
Manual shimming within the voxel resulted in water linewidths $\leq 11$ Hz. Following flip angle, water suppression, and RF pulse power optimization using automated methods, the 2-D J-resolved sequence collected 48 TE-stepped spectra from the voxel, with the echo time ranging from 30 to 500 ms in 10-ms increments. Acquisition parameters were TR = 2.0 s, acquisition bandwidth = 2 kHz, repetitions = 16, nominal voxel volume = 8 cc and approximate scan duration = 28 min.

This process was repeated on a $2 \times 2 \times 2$-cm$^3$ parieto-occipital cortex voxel. On midsagittal images, we aligned the ventral edge of the voxel with the dorsal corner of the splenium of the corpus callosum, covering posterior cingulate and retrosplenial cortices, and positioned the voxel on the midline in axial images (Figure 1). As POC spectral quality was superior, eight repetitions were obtained in $\sim 14$ min. Total time in the magnet was 75–90 min.

**MRS data processing and analysis.** All MRS processing was performed blind to diagnosis. Real (not magnitude) spectra were used (Figure 2). For each voxel, the 24 TE-stepped free-induction decays were zero-filled to 128 free-induction decay in f1. We used the commercial spectral fitting package LC Model (version 6.1-4E, Oakville, Ontario, Canada) to fit every J-resolved spectral extraction within a bandwidth of 50 Hz ($-25$ to $+25$ Hz). We used GAMMA to generate sets of 48 point-resolved spectroscopy sequence, TE-stepped spectra ranging from 30 to 500 ms in 10-ms increments. For every metabolite, we fit its spectrum over the 2-D-fitting procedure, we determined an average CRLB value weighted by the signal-to-noise ratio of each spectral extraction on the basis of the N-acetylaspartate (NAA) resonance. When a voxel location by mood state interaction was incorporated into the model, we assessed the effect of mood state (mania versus euthymia) and voxel location (ACC vs POC) on glutamine/glutamate, NAA/Cr and lactate/Cr measures using a General Linear Model analysis fit using the Mixed routine in SPSS statistical software (SPSS, Chicago, IL, USA) with age, gender and GM% as covariates. Main effects and voxel location by mood state interaction were explored. Significance was fixed at $p = 0.05$. We examined the effects of gender and medication (that is, medicated status versus unmedicated status for benzodiazepines, for lithium, and for anticonvulsants) on metabolite ratios using one-way analysis of variances. We calculated correlation coefficients for the relationships between age, voxel GM% and CPZ equivalents with metabolite/Cr values. Finally, we examined MADRS, YMRS and PANSS score correlations with metabolite/Cr values.

**Image segmentation.** Tissue segmentation of T1-weighted images into GM, white matter and cerebrospinal fluid in each MRS voxel was calculated using Matlab (Natick, MA, USA) and the SPM toolbox (Cambridge, UK). The percentage of GM in ACC and POC was 56.0 $\pm 5.7\%$ and 49.1 $\pm 7.6\%$ (BD-maniac), 58.1 $\pm 4.1\%$ and 53.8 $\pm 5.1\%$ (BD-euthymic), 60.3 $\pm 2.4\%$ and 57.7 $\pm 2.9\%$ (controls) while that of white matter was 23.5 $\pm 3.6\%$ and 38.5 $\pm 7.8\%$ (BD-maniac), 20.5 $\pm 4.1\%$ and 35.7 $\pm 5.1\%$ (BD-euthymia), 22.0 $\pm 6.5\%$ and 30.6 $\pm 3.0\%$ (controls), respectively. There was no statistically significant difference in GM% between the bipolar patients in the euthymic state and in the manic state in the ACC ($p = 0.44$) or POC ($p = 0.19$). Nor was there any statistically significant difference in GM% between the bipolar patients in the euthymic state and HC subjects in the ACC ($p = 0.26$) or POC ($p = 0.17$).

**Statistical analysis.** Given the prior literature on metabolic dysfunction in bipolar disorder and specific findings on lactate, glutamine/glutamate ratio and NAA in manic or mixed states, we assessed the effect of mood state (mania versus euthymia) and voxel location (ACC vs POC) on glutamine/glutamate, NAA/Cr and lactate/Cr measures using a General Linear Model analysis fit using the Mixed routine in SPSS statistical software (SPSS, Chicago, IL, USA) with age, gender and GM% as covariates. Main effects and voxel location by mood state interaction were explored. Significance was fixed at $p = 0.05$. We examined the effects of gender and medication (that is, medicated status versus unmedicated status for benzodiazepines, for lithium, and for anticonvulsants) on metabolite ratios using one-way analysis of variances. We calculated correlation coefficients for the relationships between age, voxel GM% and CPZ equivalents with metabolite/Cr values. Finally, we examined MADRS, YMRS and PANSS score correlations with metabolite/Cr values.

**Results**

For Lac/Cr there was a main effect of clinical state ($F(1,5) = 33.296, p = 0.002$) but no main effect of voxel location ($F(1,5) = 0.908, p = 0.383$). When a voxel location $\times$ clinical state interaction was incorporated into the model, there was a main effect of clinical state ($F(1,6) = 8.972, p = 0.026$) but no main effect of voxel location ($F(1,6) = 0.08, p = 0.785$) nor a voxel location $\times$ clinical state interaction ($F(1,6) = 0.001, p = 0.981$). Specifically, Lac/Cr values were 36% lower in the euthymic state than in the manic state (Figure 3).
For the Gln/Glu ratio there was a main effect of clinical state \[F(1,3) = 10.923, P = 0.043\] but no main effect of voxel location \[F(1,4) = 0.067, P = 0.808\]. When a voxel location \times clinical state interaction was incorporated into the model, no significant differences were seen in Gln/Glu ratio between clinical states \[F(1,3) = 2.369, P = 0.225\]. There remained no significant effect of voxel location \[F(1,5) = 0.365, P = 0.578\].

For NAA/Cr there was no main effect of clinical state \[F(1,6) = 4.18, P = 0.090\]. There was a significant effect of voxel location \times clinical state interaction was incorporated into the model, no significant differences were seen in NAA/Cr ratio between clinical states \[F(1,6) = 2.369, P = 0.225\]. When a voxel location \times clinical state interaction was incorporated into the model, no significant differences were seen in NAA/Cr ratio between clinical states \[F(1,3) = 2.369, P = 0.225\]. When a voxel location \times clinical state interaction was incorporated into the model, no significant differences were seen in NAA/Cr ratio between clinical states \[F(1,3) = 2.369, P = 0.225\].

Discussion

To our knowledge this is the first longitudinal $^1$H-MRS study across mania and euthymia of patients diagnosed with bipolar disorder type I. Patients diagnosed with bipolar disorder type I demonstrated a state related change in brain lactate concentration with euthymic subjects showing a significantly lower lactate signal compared with the same subjects in a manic state. When compared with age- and gender-matched

![Figure 2](https://example.com/image2.png)

**Figure 2** Contour plots of real two-dimensional (2-D) spectra from the anterior cingulate cortex (ACC) in a control (top) and bipolar disorder (BD) subject (bottom). In each case, the X axis is frequency (F2 in p.p.m.) and the Y axis is J (F1 in Hz). The spectral region from about −35 to +35 Hz is shown. The main metabolite resonances recognizable in the plots are labeled. Although the lactate resonance is not well-resolved in these plots, its approximate location at 1.33 p.p.m. is highlighted. The additional information available from 2-D magnetic resonance spectroscopy (MRS) allows improved fitting of this metabolite as discussed in the text. Note the variable nature of water suppression, and of the macromolecule signal profile (highlighted in a box in the top panel) in the two spectra. Lac, lactate; H2O, water; GSH, glutathione; MMs, macromolecules.
membrane metabolism. Kato and Kato hypothesized that bipolar disorder is characterized by a trait metabolic dysfunction that is demonstrated in the abnormal findings observed in euthymia. They conjectured that the brain’s attempts to ‘correct’ these abnormalities through increased monoamnergic neurotransmission might induce pathological mood states such as depression or mania. In other words, neither mood episodes nor euthymia are truly healthy states in bipolar disorder. Rather, they represent varying degrees of compensation to underlying abnormalities.

In examining the effect of clinical state on other metabolites it is worth noting that the Gln/Glu ratio demonstrated a significant (P = 0.046) effect of clinical state. This finding did not meet criteria for significance when corrected for multiple comparisons (adjusted α = 0.016), nor was there a significant effect of clinical state when state by anatomical region interaction was incorporated into the model. Nevertheless, this result suggests that Glu/Glu ratio abnormalities previously observed in bipolar disorder may in fact vary with clinical state. This finding bears further investigation.

The strengths of this study include the investigation of inpatients who are highly resistant to engage in research studies, the longitudinal design and the assessment of both euthymic and manic states in the same individuals, a challenging task. All of our subjects were scanned on the same high field (4T) magnet at both time points and we have included a control population. Medication regimens were relatively consistent at both time points.

One limitation of our study is a small sample size that makes it difficult to rule out type I errors. This applies both to patients as well as HC subjects whose small numbers represent an attempt to provide a match for age and gender to the patient population. Another limitation is the generalizability of these findings. Although manic state scans were all acquired in a population symptomatic enough to require inpatient hospitalization, the patients who were able to complete the manic state scan were generally less symptomatic than those who could not complete the scan. Additionally, at the time of the euthymic state, all subjects were in ongoing psychiatric treatment, free of substance abuse or dependence and were able to be contacted and perform the follow-up study as outpatients. It is possible that these patients may have better inter-episode functioning and better prognosis thereby limiting generalization to the bipolar disorder population as a whole. Finally, although we cannot rule out an effect of medications on our findings, the longitudinal nature of this experiment was designed to minimize differences in medication regimens at both time points.

This demonstration of a relationship between metabolic dysfunction and mood state has implications for both the diagnosis of bipolar disorder as well as its treatment. Epidemiological studies demonstrate that at least 20% of patients hospitalized for unipolar depression will go on to have a diagnosis of bipolar disorder type I. The development of a biomarker measurable at hospitalization that can differentiate euthymia in bipolar disorder versus unipolar depression would be of significant diagnostic and predictive value. Similar studies are needed to compare brain lactate in both bipolar disorder as well as unipolar depression across depressive and euthymic states.
The demonstration of a biomarker intimately related to clinical state will possibly allow evaluation of novel therapies. Notably, Kim et al. have already performed a study examining both symptomatology score changes we well as changes in lactate in response to quetiapine. Although Kim et al. did not follow patients to euthymia; they did note a significant association between change in lactate level and clinical response. This finding may be extended to other interventions and may allow for the early differentiation of patients who will achieve response from those who will remain symptomatic.

Conflict of interest
Dr Renshaw is a consultant to Novartis, GlaxoSmithKline and Kyowa Hakko. Dr Öngür is PI on a research contract with Rules Based Medicine Inc. The other authors declare no conflict of interest.

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