HHS Public Access

Author manuscript

J Clin Psychopharmacol. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

J Clin Psychopharmacol. 2017 February ; 37(1): 40–45. doi:10.1097/JCP.0000000000000616.

Increased Brain Lactate during Depressive Episodes and Reversal Effects by Lithium Monotherapy in Drug-Naive Bipolar Disorder: A 3T 1H-MRS Study

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Abstract

Objective—Mitochondrial dysfunction and energy metabolism impairment are key components in the pathophysiology of bipolar disorder (BD) and may involve a shift from aerobic to anaerobic metabolism. Measurement of brain lactate *in vivo* using proton magnetic resonance spectroscopy (1H-MRS) represents an important tool to evaluate mitochondrial and metabolic dysfunction during mood episodes as well as to monitor treatment response. To date, very few studies have quantified brain lactate in BD. In addition, no study has longitudinally evaluated lactate using 1H-MRS during depressive episodes or its association with mood stabilizer therapy. This study aimed to evaluate cingulate cortex (CC) lactate using 3T 1H-MRS during acute depressive episodes in BD and the possible effects induced by lithium monotherapy. The association between brain lactate with mitochondrial activity and antidepressant efficacy were also assessed.

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DECLARATION OF INTEREST

A patent for the use of ketamine in depression has been awarded that lists Dr. Zarate among the inventors; he has assigned his rights on the patent to the US government, but will share a percentage of any royalties that may be received by the government. All other authors declare no potential conflict of interest.

Methods—Twenty medication-free outpatients with short length of illness BD (80% drug-naive) in a current major depressive episode were matched with healthy controls. Patients were treated for 6 weeks with lithium monotherapy at therapeutic doses in an open-label trial (blood levels 0.48±0.19mmL). CC lactate was measured before (week 0) and after lithium therapy (week 6) using 1H-MRS. Antidepressant efficacy was assessed with the 21-item Hamilton Depression Rating Scale as the primary outcome.

Results—Subjects with BD depression showed a significantly higher CC lactate in comparison to healthy controls. Furthermore, a significant decrease in CC lactate was observed after 6 weeks of lithium treatment compared to baseline (p=0.002). No association between reduction in CC lactate levels over time and remission at week 6 was observed.

Conclusions—This is the first report of increased CC lactate in patients with bipolar depression and lower levels after lithium monotherapy for 6 weeks. These findings indicate a shift to anaerobic metabolism and a role for lactate as a state marker during mood episodes. Energy and redox dysfunction may represent key targets for lithium's therapeutic actions.

Clinical trial number NCT01919892

Keywords

Bipolar disorder; depression; lithium; lactate; treatment; imaging

INTRODUCTION

Energy metabolism dysfunction has been considered a key component of the pathophysiology of Bipolar Disorder (BD) [1, 2]. Evidence for this metabolic dysfunction includes lower brain intracellular pH and phosphocreatine in BD[3]. Brain lactate has a key role in neural energy metabolism and its altered concentrations may represent a less severe form of mitochondrial and metabolic dysfunction[4,5]. In addition, different line of evidence showing increased oxidative stress [6,7] and impaired expression of mitochondrial genes in BD[8,9] further support the role of mitochondrial and redox dysfunction leading to a shift towards anaerobic metabolism and associated elevated risk for cellular injury[10,11].

Proton magnetic resonance spectroscopy (1H-MRS) provides a non-invasive technique to measure brain lactate *in vivo* in psychiatric research. In BD, previous studies during mood episodes (manic and depressed) and euthymia have shown mixed results [5, 12, 13]. In a cross-sectional study, Dager et al[5] found an increase in gray matter lactate concentrations in medication-free BD patients with long-term illness and predominantly in a depressed or mixed state. Brady et al[13] found similar lactate levels in the anterior cingulate cortex (CC) during mania (n=15) compared to healthy controls. Seven patients underwent a subsequent follow-up scan (average follow-up time: 21.1 months) while in euthymia and medicated, and showed lower anterior CC lactate compared to matched controls. This is a key area involved in mood regulation and is a target for lithium and antidepressants biological effects[14]. A recent study emphasized that lactate is primarily localized in the CC (and caudate) of subjects with BD[15].

Lithium is the mainstay of pharmacotherapy for acute mood episodes, prophylactic treatment, and suicide prevention in BD[16]. Data from the European drug surveillance program describe that lithium is the most frequently prescribed agent for bipolar depression in combined therapy (33%)[17]. Lithium modulates key mitochondrial proteins and prevents and/or reverses DNA damage, free radical formation and lipid peroxidation[16, 18, 19]. Lithium has also been shown to improve synaptic strength, cellular resilience and glial function, and induce a significant increase in mitochondrial complex I activity[11, 20]. Interestingly, in a cross-sectional MRS study, Friedman et al[21] described similar brain lactate concentrations in BD subjects taking lithium compared to healthy controls. In mania, Kim et al[12] observed a significant decrease in midfrontal cortex lactate in subjects with BD treated with quetiapine for 12 weeks; this finding was associated with the antimanic response. However, no study has longitudinally assessed the effects of lithium on brain lactate concentrations during mood episodes in BD.

In the present study, CC lactate was evaluated in medication-free BD subjects in a major depressive episode before and after 6 weeks of lithium monotherapy using 3T 1H-MRS. Furthermore, although a few studies evaluated brain lactate in BD, no study has either longitudinally evaluated lactate using 1H-MRS during a specific mood state (mania or depression) or assessed its association with lithium monotherapy treatment response in drug-naïve BD subjects.

We hypothesized that BD subjects would have increased lactate in the CC, as measured by multivoxel 3T 1H-MRS during bipolar depression compared to healthy controls, and that reductions in lactate with lithium treatment would be associated with treatment response.

METHODS

Participants

Fifty-nine individuals pre-screened by phone interviews were evaluated at the outpatient clinic of the Mood Disorders Group (LIM-27), Department and Institute of Psychiatry, University of São Paulo. Twenty-six subjects fulfilled criteria for the present study and were enrolled. Six BD subjects were excluded due to the following reasons: two patients dropped-out before the completion of a 6-week follow-up, while four subjects had technical issues (data collection) at either baseline or follow-up 1H-MRS scan, which limited a complete post-processing data analysis. Thus, our final sample consisted of 20 medication-free subjects (80% treatment-naïve) with BD in a major depressive episode (16 females and 4 males, aged 22–43 years old) who completed the 6-week lithium trial.

Subjects with BD in a depressive episode were included according to the following criteria: (a) age between 18 and 45 years, (b) diagnosis of BD I or II in a current major depressive episode according to the DSM-IV, (c) score greater than 17 in the 21-item Hamilton Depression Rating Scale (HDRS)[22], (d) no previous use of lithium (lifetime) and absence of the use of any psychiatric medication or drugs with CNS effects for at least 6 weeks, and (e) illness duration of no more than 5 years. Exclusion criteria included rapid cycling BD, current substance (including alcohol) abuse or dependence, with the exception of tobacco, previous electroconvulsive therapy, presence of neurological disorders or any medical

disorder that could affect the CNS, mental retardation, medications with CNS effects, vitamins and contraindications for MRI scanning[23].

Patients were evaluated with a semi-structured clinical interview and blood tests (including complete blood count, electrolytes, renal and thyroid function). All patients were started on lithium carbonate (450mg/day) and a systematic follow-up was carried out for 6 weeks. Visits for clinical assessment and plasma lithium monitoring in the plasma were performed at weeks 1, 2, 4 and 6. Subsequent dose adjustment was allowed, based on individual clinical efficacy and aiming to reach therapeutic levels of lithium (0.4–1.0mmL). The 1H-MRS scanning was performed at baseline (week 0) and endpoint (week 6) in BD patients and only at baseline in the matched control group.

The healthy volunteers group included 16 subjects (9 females and 7 males, aged 20–43 years old), all free of any psychiatric disorder (based on DSM-IV criteria) and with no history of mental disorders among first-degree relatives. Volunteers were recruited through advertisement in the local community. The local institutional review board approved this study and all subjects provided informed written consent prior to participating in the study. This study was part of a multimodal investigation to evaluate central and peripheral therapeutic targets of lithium's antidepressant actions in Bipolar Disorders.

Clinical Measures

Experienced psychiatrists performed all clinical assessments. Psychiatric evaluation was performed in both patients and healthy controls using the Structured Clinical Interview (SCID-I/P) for DSM-IV[24]. A past medical history was obtained directly from each participant and/or family member. At each follow-up visit (weeks 1, 2, 4 and 6), the severity of depressive and manic symptoms was assessed using, respectively, the HDRS and the Young Mania Rating Scale (YMRS)[25]. Clinical response was defined as a decrease ≥ 50% in the HDRS, while remission as a HDRS and YMRS score ≤ 8. The global functioning at baseline and endpoint (improvement) was also assessed using the Clinical Global Improvement (CGI) scale26. Inter-rater reliability was over 0.9 for all rating scales.

Proton Magnetic Resonance Imaging and Spectroscopy (1H-MRS) Scan and data processing

All 1H-MRS sequences were performed using a 3T magnet (Intera Achieva, Philips, Best, Netherlands) and an eight-channel head coil. Metabolite concentrations of lactate were obtained using a 2D-MRS Imaging (MRSI) PRESS sequence (TE/TR=288/1500 ms) with a slice thickness of 2cm, FOV=20cm and a matrix of 20 × 20, resulting in individual voxel sizes of 2 cm^3. Twelve individual voxels (2 columns of 6 voxels each) placed on the CC, as shown in Figure 1A, were selected for analysis. The MRS grid was placed on an axial slice just above the corpus callosum, following the AC-PC angulation. The 12 individual spectra within the selected region of interest (ROI) were averaged and processed as a single spectrum. This method was shown to obtain significantly improved lactate measurement as compared to averaging chemical concentrations derived from the fitting of individual voxels in the ROI[27]. Spectral peak quantification was performed using the Spectroscopy Tool of the Extended MR Workspace R.2.6.3.5 (Philips Medical Systems, Best, The Netherlands) after

phase adjustment, exponential line broadening of −1Hz, and zero-filling. The spectrum was fitted to the sum of four signals: choline, creatine, N-acetyl-aspartate and the lactate double peak (Figure 1B). MRSI was acquired at a long TE (288ms), to ensure that lipid and macromolecule signal were fully relaxed and did not overlap with the lactate signal. Lactate was quantified by the integral ratio of the lactate peak with the creatine peak. Quality criteria used for spectra inclusion were based on signal to noise ratio (SNR) measurements. Since lactate appears as an isolated peak with no overlap with other metabolite signals on a spectrum with a TE of 288ms, SNR is a convenient rejection criterion[28]. To investigate the brain tissue composition of the ROI, three-dimensional volumetric images were obtained using the 3D-T1FFE technique (FA=8°; TE/TR/TI=3.2/7/900 ms) with isotropic resolution of 1 mm^3. Briefly, the brain tissue was extracted using the brain extraction tool (BET) and segmentation into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) was achieved using the automated brain segmentation tool FAST, both apart of the FSL suite (http://www.fmrib.ox.ac.uk/fsl). Finally, the ROI was overlaid on the segmented image using a Python-based script developed in-house and percentages of WM, GM and CSF were calculated for each ROI. The scanner used for this study is submitted to a weekly MRS quality control performed using a phantom with an aqueous solution of brain metabolites. The focus of this study was lactate. The long TE MRSI acquisition used was chosen on purpose to measure a significantly high lactate signal, which otherwise is not observable in a single voxel conventional MRS spectrum. The disadvantage of this long TE acquisition is that short T2 metabolites, such as mI and Glx are not measurable. For this purpose we conducted a different MRS acquisition in the same population, which has already been published (29) and reporting results on all other metabolites.

Blood sampling and laboratorial analysis

Samples were centrifuged with Ficoll (Sigma) at 20 °C at 700 × *g* for 40 min and mononuclear cells were separated by Ficoll gradient to obtain leukocytes. The plasma (first layer) was removed; leukocytes (second layer) were gently washed twice with phosphate-buffered saline (PBS) and centrifuged at 20 °C and 700× *g* for 15 min. After centrifugation, PBS and dimethyl sulfoxide (DMSO) <0.01 % were added to the samples that were progressively frozen at 10 °C for 30 min, at 20 °C for 30 min, and finally stored at 80 °C until assays were carried out. All samples were evaluated in duplicates.

Statistical Analysis

The Kolmogorov-Smirnov test was used to verify the normality of the data within each study group. Between-group comparisons of continuous variables with a Gaussian distribution were performed with unpaired two-tailed Student's t-test, while the Mann-Whitney test was used for non-parametric data. The chi-square test was used for the comparison of categorical variables. Changes in CC lactate and depressive symptoms over time were assessed with the paired-samples t-test (normal distribution) or with the non-parametric Wilcoxon Rank Test (non-normal distribution). Specifically for the comparison of CC lactate between BD patients both at baseline and at week 6 as well as controls, the analysis of covariance (ANCOVA) was carried out controlling the CSF fraction of the voxel as a covariate. Mixed-effects models were also used to investigate whether clinical variables and outcomes were associated with changes in brain lactate (dependent variable) after 6 weeks of lithium

treatment. Finally, the correlation between brain lactate and clinical variables were evaluated using partial correlations controlling for the CSF fraction of the voxel. Pearson's correlation coefficients or Spearman's tests were used for additional correlations. All statistical analyses were performed using SPSS 21.0 with a significance level set at <0.05 (two-tailed).

RESULTS

Demographic and Clinical data

Demographic and clinical data for subjects with BD and healthy controls are summarized in Table 1. No significant difference in age (p=0.29) or gender (p=0.12) was observed when comparing BD subjects and healthy controls. All patients were free of any psychotropic medication for at least 6 months prior to the enrollment in the study and 16 (80%) had never received treatment with any mood stabilizer or antipsychotic agent (treatment-naïve). Mean lithium levels at week 6 were 0.48±0.19mmL. All patients were using therapeutic doses of lithium (600–900mg/day; mean dose 671.1±115mg). All patients had less than 5 years of illness duration (mean=36.0±18.7 months).

Furthermore, there were significant changes in HDRS (baseline=22.40±3.01 and endpoint=7.90±6.23, p<0.001) and CGI scores (baseline=4.00±0.32 and endpoint=2.15±0.87, p<0.001) (Table 1). Twelve BD patients (60%) achieved remission at endpoint. No treatment-emergent affective switches or dropouts were observed.

Cingulate cortex lactate in Bipolar Depression versus Healthy Controls

BD subjects in a depressive episode showed at baseline increased lactate in the CC compared to healthy controls (F=4.32, df=1, p=0.04; general linear model with the CSF fraction of the voxel as a covariate) (Table 2). CSF fraction of the ROI also did not significantly vary across groups (BD patients= 0.17±0.05 vs. controls=0.19±0.06; t=1.16, df=34, p=0.25). No difference between groups was also observed for WM (t=0.9, df=23, p=0.37) and GM (t=1.32, df=23, p=0.2) fractions of the ROI. No changes in CC lactate levels were observed when comparing drug-naïve versus drug-free BD subjects (data not shown). CC Lactate at baseline was not associated with any clinical outcome (total improvement, response or remission).

Cingulate cortex lactate in Bipolar Depression at Baseline compared to Post-Lithium

A significant reduction in CC lactate was observed in BD patients after 6 weeks of lithium treatment compared to baseline (t=−3.52, df=19, p=0.002) (Table 2, Figure 2). After lithium treatment BD patients showed no difference of CC lactate when compared to healthy controls (F=2.58, df=1, p=0.11). When comparing patients pre vs. post lithium treatment, no changes in CSF (t=−0.98, df=19, p=0.33), GM (t= 1.64, df=19, p=0.11) or WM (t= −1.145, df=19, p=0.16) were observed.

Predictors of response

Baseline CC lactate did not correlate with any demographic and clinical variable described in Table 1 (partial correlation controlled for the CSF fraction of the voxel) (all p=n.s), except for a positive association with family history of mood disorders (p=0.02, r=0.46). No

significant correlations were observed between changes in CC lactate and HDRS and CGI scores over time or at endpoint (all p=n.s). Mixed effects model analysis revealed no significant association between remission status at endpoint and the change in CC lactate over time (F=1.62, p=0.211).

Associated biological findings

Changes in lactate was not associated with clinical improvement (HDRS score change) (p=0.5). Plasma lithium at endpoint was not associated with lactate at endpoint (week 6) (p=0.2) but was negatively associated with changes in lactate levels over time (p=0.04, r= −0.43).

DISCUSSION

To the best of our knowledge, our study is the first longitudinal 1H-MRS study to evaluate CC lactate concentrations in medication-free patients with acute bipolar depression before and after treatment with lithium. As hypothesized, based on evidence supporting a key role for brain energy metabolism dysfunction with a shift towards anaerobic metabolism in BD[2, 20], we found increased CC lactate levels in subjects with BD during a depressive episode compared to matched healthy controls. The CC is part of the frontal–subcortical circuit that has a critical role in mood regulation in BD. Similar to our findings, Dager et al.[5] described an increase in gray matter lactate in an axial section focused around the anterior cingulate in BD, which was not associated with improvement in depression[5]. Likewise, in a recent study using 2D 1H-MRS, a significant increase in brain lactate in medication-free BD subjects in mania (n=12) and Bipolar depression (n=12) was found regardless of the brain region when compared to healthy controls[30]. In the same context, decreased frontal lobe pH was observed in BD patients and has been directly associated with lactic acidosis[1]. Indeed, cytosolic production of lactate is regulated by mitochondrial oxidative processes occurring during pathological conditions such as acute mood episodes. The elevated conversion of glucose to lactate implies that little glucose is available for biosynthesis or mitochondrial oxidation and that lactate may serve as a metabolic substrate to neurons. In this circumstance, lactate is taken up and used in highly oxidative neurons due to changes in mitochondrial redox status. This shift aims to provide supplementary fuel source to neural cells.

In contrast to a previous study showing no changes in brain lactate levels in BD subjects taking lithium over time[21], our study found a significant decrease in CC lactate concentrations after 6 weeks of lithium monotherapy. In Friedman et al[21], subjects with BD were not evaluated under a specific duration of treatment or mood state, which may account for the difference with the present study in terms of the longitudinal effects of lithium. However, similar to our findings, they showed no differences in brain lactate levels in BD subjects taking lithium compared to healthy controls. Despite no statistical significance, lactate post-treatment was lower (0.14) compared to controls (0.18), which could be due to lithium-inducing hypernormalization of brain lactate. The observed beneficial actions of lithium on reducing anaerobic metabolism may contribute to the well-known neuroprotective effects of this agent[31]. In addition, evidence supports the role of lithium as a key modulator

of mitochondrial function and cellular energy metabolism[18, 19, 20], which was supported by the present findings. Lithium also seems to normalize these changes by shifting back to glycolysis, limiting lactate production and improving mitochondrial respiration[11]. It may be hypothesized that the effects of lithium on brain energy production underlie at least in part its antidepressant and mood stabilizing properties. Our results suggest that lithium acts by reducing the shift from aerobic to anaerobic metabolism observed in BD[11,32]; however this shift did not correlate with clinical improvement. One explanation is the considerable number of good responders to lithium in the present sample, based on a potential enriched sample selected which aimed to allow the use of lithium monotherapy and to avoid possible dropouts due to non-response. The small number of non-responders may have precluded the ability to detect differences in mean lactate levels.

The strengths of this study include the longitudinal design with both clinical and imaging measurements and the sample size is one of the largest within-subjects in BD. The study has homogeneous duration of treatment, specific use of lithium monotherapy, exclusion of comorbid conditions (e.g. substance abuse/dependence) and all BD patients are drug-free (80.0% of whom were treatment-naïve). In addition, the fact that we recruited a sample with a relative short duration of illness (mean of 36 months) and no concurrent substance use disorders limits the possibility that our results could have been influenced by confounding factors, such as illness staging and/or co-occurring long-term comorbidities. Differently from the previous studies that assessed brain lactate levels in subjects with BD[5,12,13], we employed a within-subject longitudinal design with a systematic clinical follow-up in which the 1H-MRS exams were repeated after a specific period of time. Finally, the use of a long echo time improves the resolution of the lactate resonance and summing across voxels improves the SNR. Furthermore, it needs to be pointed that we are reporting relative ratios of lactate to Cr signals and not absolute concentrations, so any changes in these ratios could be theoretically also related to changes in Cr or metabolite relaxation times. However, this is very unlikely. An extensive and thorough study[5] measuring absolute metabolite concentrations and T2 relaxation times in different brain regions with different tissue compositions concluded that there were no differences between BD medication free patients and healthy controls in Cr, Cho, NAA and mI concentrations or relaxation times. The only differences were found for lactate and Glx concentrations. Therefore to measure lactate relative to Cr is a common practice, and has been used previously to measure longitudinal lactate changes in BD patients[13]. Some limitations in our study merit discussion. First, the duration of lithium treatment was relatively short. However, most potential good responders to lithium had achieved a response and most had mild to moderate depression at baseline. In addition, this was an open-label trial, which might limit potential conclusions that can be drawn from clinical outcomes (which could be related to lithium's effects or natural course of illness). Second, we enrolled a convenience sample that could have selected good or excellent lithium responders. Lastly, our study was uncontrolled and healthy volunteers only had one scan.

Overall, our findings reinforce the presence of altered metabolic activity in the brain leading to a shift towards lactic acidosis during mood episodes. It is also supported a key role for lithium in normalizing this dysfunctional brain energy state through direct effects at mitochondrial function. The present findings reinforce that lactate may be a state biomarker

in BD and that mitochondrial modulators might offer promising treatment targets in the illness, especially in long-term treatment. Further studies with longer duration and larger samples are required to provide further evidence for the key mechanisms of lithium's modulatory effects on brain mitochondrial and redox activity in BD and its association with clinical outcomes.

Acknowledgments

FUNDING

This study was sponsored by Sao Paulo Research Foundation (Fapesp, Brazil, 2009/14891-9, RM-V). The Laboratory of Neuroscience, LIM27, is also supported by the Associação Beneficente Alzira Denise Hertzog da Silva (ABADHS) and JNK Empreendimentos e Incorporações.

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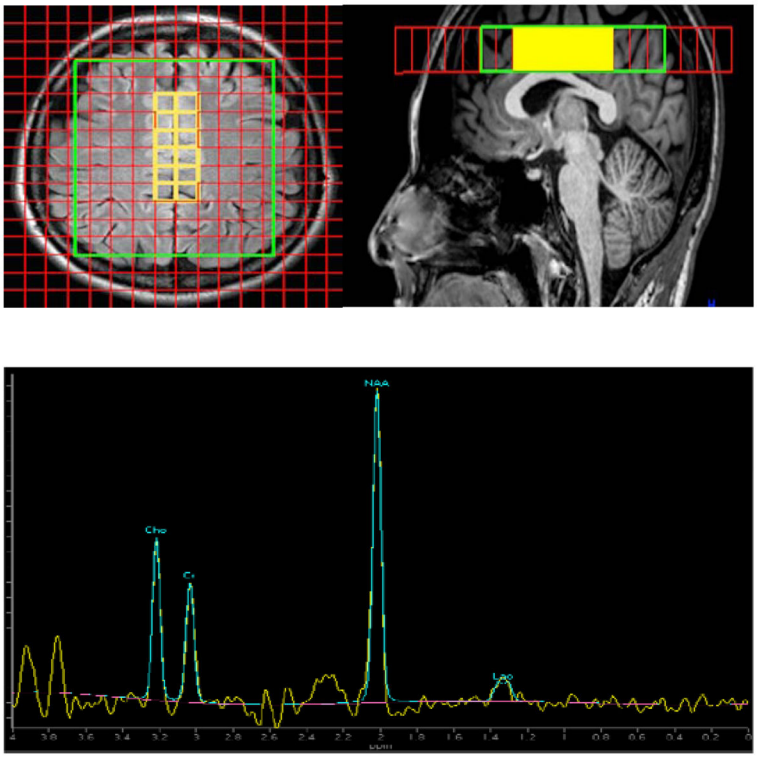

Figure 1.

Figure 1A. Axial and sagital view of the two-dimensional matrix acquired by the MRSI sequence. The green line indicates the region selected for magnetic field homogenization purposes. Signal from outside this region was suppressed to avoid contamination. The individual spectra of the voxels in yellow (axial view) were all summed up to study a single ROI placed on the cingulate cortex (yellow ROI on sagital view).

Figure 1B. Original spectrum in yellow and fitted line of the Lactate, NAA, Cr and Cho signals in blue.

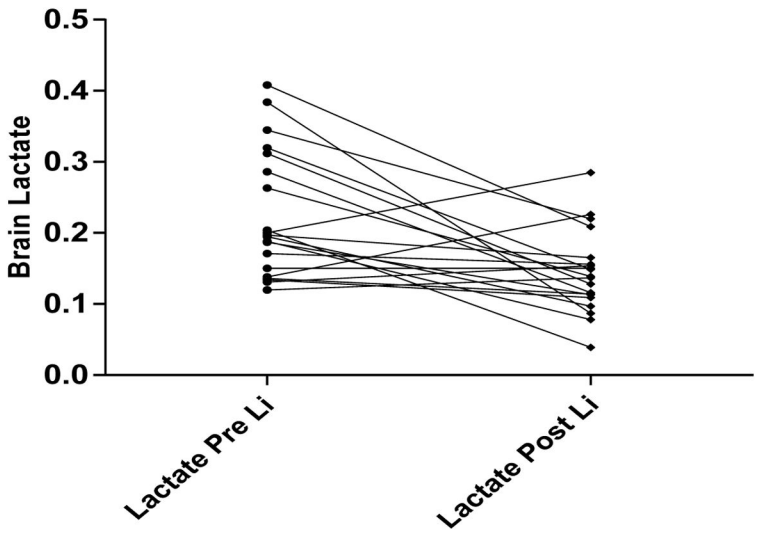

Figure 2.

Individual changes in brain lactate from baseline (depressive episode) to endpoint (after 6 weeks of lithium (Li) monotherapy in drug-naïve BD). Brain Lactate presented in mmol/L.

Table 1

Demographic and clinical information of patients with bipolar disorder (BD) and healthy controls

	Bipolar disorder (n=20)	Healthy controls (n=16)	Statistical tests
Age (mean±SD)	28.8±5.4	26.8±6.1	t=−1.06, df=34, p=0.297
Gender (no. females;%)	16 (80.0%)	9 (56.2%)	χ^2=2.36, df=1, p=0.124
BD subtype (no. type II; %)	14 (70.0%)	-	-
Duration of Illness (months; mean±SD)	36.0±18.7	-	-
Treatment-naïve (n; %)	16 (80.0%)	-	-
History of Psychosis (n; %)	1 (5.0%)	-	-
Serum lithium levels at week 6 (mmol/L; mean±SD)	0.48±0.19	-	-
Lithium final dose (mg)	671.1±115	-	-
Response rate at Week 6 (n; %)	17 (85.0%)	-	-
Remission rate at Week 6 (n; %)	12 (60.0%)	-	-
HDRS scores (mean±SD)	22.40±3.0	7.90±6.23	**p<0.001**
CGI scores (mean±SD)	4.00±0.32	2.15±0.87	**p<0.001**

BD, bipolar disorder; HDRS, 21-item Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale. CGI, Clinical Global Improvement scale.

Table 2

Brain lactate before (week 0) compared to**: A)** after (week 6) lithium monotherapy in patients with depression in Bipolar Disorder and **B)** matched healthy controls

A)	**BD Week 0**	**BD Week 6 (Li)**	**(paired-t-test)**
Brain lactate, mmol/L (/Cr) (mean±SD)	0.223±0.09	0.143±0.05	t=−3.52, df=19, p=0.002

B)	**BD Week 0**	**Controls**	**(unpaired t-test)**
Brain lactate, mmol/L (/Cr) (mean±SD)	0.223±0.09	0.181±0.04	F=4.32, df=1, p=0.04