Journal of Affective Disorders 206 (2016) 315–320

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Trait-related alterations of N-acetylaspartate in euthymic bipolar patients: A longitudinal proton magnetic resonance spectroscopy study

Burç Aydin [a,*], Ayşegül Yurt [b], Necati Gökmen [c], Perry Renshaw [d], David Olson [e], Ayşegül Yildiz [f,g]

[a] Department of Medical Pharmacology, School of Medicine, Dokuz Eylul University, Balcova 35340, Izmir, Turkey
[b] Department of Medical Physics, Health Sciences Institute, Dokuz Eylul University, Izmir, Turkey
[c] Department of Anesthesiology and Reanimation, School of Medicine, Dokuz Eylul University, Izmir, Turkey
[d] University of Utah, The Brain Institute & Department of Psychiatry, Salt Lake City, UT, USA
[e] Harvard Medical School, McLean Hospital, Brain Imaging Center, Belmont, MA, USA
[f] Department of Psychiatry, School of Medicine, Dokuz Eylul University, Izmir, Turkey
[g] International Consortium for Bipolar Disorder Research & Psychopharmacology Program, McLean Division of Massachusetts General Hospital, Boston, MA, USA

ARTICLE INFO

Article history:
Received 27 May 2016
Received in revised form
27 July 2016
Accepted 8 September 2016
Available online 9 September 2016

Keywords:
N-acetylaspartate
Magnetic resonance spectroscopy
Mania
Euthymia
Dorsomedial prefrontal cortex

ABSTRACT

Background: Neurochemical changes are responsible for bipolar disorder (BD) pathophysiology. Despite current progress in BD research, mood- and trait-related alterations in BD continue to elicit further investigation.
Methods: In this study, we report a longitudinal proton magnetic resonance spectroscopy study evaluating dorsomedial prefrontal cortex (DMPFC) metabolites N-acetylaspartate (NAA), creatine plus phosphocreatine (total creatine [tCr]), phosphorylcholine plus glycerophosphocholine, myo-inositol, and glutamate plus glutamine levels of manic and euthymic adult BD type I patients (n=48) treated with standard antimanic medicines, compared to matching healthy controls (n=44).
Results: DMPFC NAA values and NAA/tCr ratio were significantly lower in euthymic BD patients when compared with healthy controls with similar levels of other metabolites in all groups, indicating a trait-related NAA abnormality in euthymic BD patients.
Limitations: of our study include a relatively low (1.5 T) magnetic resonance field strength and variable drugs administered to achieve euthymia despite the best efforts to standardize the open fashion treatment.
Conclusions: Our study contributes to the integrating models of trait-related metabolite alterations observed in euthymia since NAA is considered as a marker of neuronal viability and mitochondrial energy metabolism. In light of supporting and conflicting results reported previously, future studies with longitudinal designs and larger patient groups are warranted to better define both state- and trait-related cerebral metabolic alterations associated with BD pathophysiology.

1. Introduction

Neurochemical alterations in bipolar disorder (BD) have been implicated as contributing to disease pathophysiology. These alterations are found in intracellular signaling pathways, hormonal signals, inflammatory processes, neuroplasticity, neurotransmitter systems, and neuronal biomarkers (Langan and McDonald, 2009; Zanetti et al., 2015). Based upon neurochemical findings, integrative theories, such as mitochondrial dysfunction and energy metabolism abnormalities in BD (Stork and Renshaw, 2005), have also been proposed to understand the basis of BD pathophysiology. Despite this progress, 'dissecting' the state- and trait-related

Abbreviations: ACC, anterior cingular cortex; BD, bipolar disorder; CGI-Mania, Clinical Global Impressions-Bipolar Version Severity of Mania; Cho, phosphorylcholine plus glycerophosphocholine; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; DSM-IV, diagnostic and statistical manual of mental disorders, 4th edition; FC, frontal cortex; FL, frontal lobe; Glx, glutamate plus glutamine; ^{1}H MRS, proton magnetic resonance spectroscopy; HAMD-17, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; mI, myo-inositol; MR, magnetic resonance; NAA, N-acetylaspartate; SCID-IV, structured clinical interview for DSM-IV; tCr, creatine plus phosphocreatine (total creatine); YMRS, Young Mania Rating Scale.

* Corresponding author.
E-mail address: burcaydin@gmail.com (B. Aydin).

http://dx.doi.org/10.1016/j.jad.2016.09.002
0165-0327/

abnormalities in BD is still a research endeavor (Langan and McDonald, 2009; Yildiz-Yesiloglu and Ankerst, 2006). Accumulating evidence from cross-sectional brain metabolism studies of BD mood states provide heterogeneous and variable results, whereas longitudinal studies in homogenous groups of BD patients are scarce (Kraguljac et al., 2012; Langan and McDonald, 2009; Moore et al., 2000; Yildiz-Yesiloglu and Ankerst, 2006).

Here we present a longitudinal proton magnetic resonance spectroscopy (^{1}H MRS) study in a cohort of BD patients in manic and euthymic mood states, examining the state- and trait-related neurochemical changes compared to healthy controls. Given the prior evidence on changes of brain metabolites in adult BD patients (Brady et al., 2012; Brambilla et al., 2004; Malhi et al., 2007; Moore et al., 2000; Yildiz et al., 2016), we examined the metabolites N-acetylaspartate (NAA), creatine plus phosphocreatine (total creatine [tCr]), and phosphorylcholine plus glycerophosphocholine (Cho) in primary analyses with myo-inositol (mI) and glutamate plus glutamine (Glx) in exploratory analyses. Our hypothesis was that manic BD patients would have lower NAA and tCr levels compared to euthymic state and healthy controls.

2. Methods

2.1. Study design

The study was designed to investigate the longitudinal changes in brain metabolites of BD patients in mania and euthymia with an age- and gender-matched healthy control group via combining clinical and imaging data of complementary studies. BD patients were subject to a clinical trial as well as an ^{1}H MRS study to test the antimanic efficacy and effects of tamoxifen treatment (ClinicalTrials.gov identifier: NCT00411203). Experimental details and results of these studies have been reported previously (Yildiz et al., 2016, 2008). Healthy controls participated in a separate ^{1}H MRS study examining the effects of midazolam-fentanyl sedation on brain chemistry (Yildiz et al., 2010).

2.2. Subjects

BD patients were 18–58 years old with a diagnosis of BD type I based on the diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV) currently in a manic or mixed state with a Young Mania Rating Scale (YMRS) (Young et al., 1978) total score >20, with or without psychotic features. Healthy controls were 17–57 years old with no DSM-IV axis I disorder, as determined by the structured clinical interview for DSM-IV (SCID-IV) non-patient version (SCID-NP). At baseline (manic state), a drug-free period was limited to one day before trial randomization. Eighty percent of the patients were on mood stabilizer and/or antipsychotic in the pretrial month (Yildiz et al., 2008). Study protocols were approved by the Turkish Ministry of Health Central Review Board and/or the Institutional Ethics Committee of Dokuz Eylul University. Written informed consent was obtained from all subjects and from at least one first-degree relatives of BD patients and the legal guardians of healthy controls below the age of eighteen.

2.3. Clinical assessment and treatment of BD patients

BD patients were assessed with ratings obtained from the YMRS (primary outcome measure), Clinical Global Impressions-Bipolar Version Severity of Mania (CGI-Mania) (Spearing et al., 1997), 17-item Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1967), and Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) in the manic state at baseline and subsequently included in a 3-week trial to receive tamoxifen or placebo per protocol (Yildiz et al., 2008). After completion of the trial, patients were given lithium (n=38; target serum levels: 0.8–1.2 mEq/L) and/or valproate (n=14; target serum levels: 50–125 mcg/mL) with or without risperidone (n=34; 1–5 mg/day), lamotrigine (n=14; 25–200 mg/day), quetiapine (n=4; 100–300 mg/day), bupropion (n=3; 150–300 mg/day), or olanzapine (n=2; 10 mg/day) as standard antimanic treatment (some patients were on more than one medication) determined by the attending physician (A.Yildiz) in an open fashion and followed up for euthymia with weekly rating scales in an inpatient stay. After the first positive assessment for euthymia, patients were discharged and followed up with rating scale assessments every two weeks to confirm 8 weeks of euthymia. Euthymia was defined as no more than three manic symptoms with a minimum or two manic symptoms with a moderate degree of severity.

2.4. MRS procedure and data analysis

The clinical trial and ^{1}H MRS experiments were conducted at the Departments of Psychiatry and Radiology, Dokuz Eylul University, Izmir, Turkey. Baseline ^{1}H magnetic resonance (MR) spectra from manic patients with BD were obtained right before trial drug administration. Following trial period, ^{1}H MR spectra of the patients having achieved euthymia for 8 weeks were obtained again (within 24 h). To enable reliable data acquisition, all BD patients and healthy controls were sedated with midazolam (0.03 mg/kg) and fentanyl (2 μg/kg) administration before all MRS scans. As reported previously, the sedation was safe and did not cause any changes in the measured metabolites of the brain (Yildiz et al., 2010). The ^{1}H MRS measurements were made on a Philips system with field strength of 1.5 T (Philips Healthcare, Best, The Netherlands). Sagittal, axial, and coronal T2-weighted cerebral images were obtained to place voxels, and single voxel short echo time MRS data were collected with a point resolved spectroscopy sequence (echo time=31 ms, repetition time=2000 ms, spectral band width 1 kHz, 1024 complex data points, 128 acquisitions) from four different brain regions, dorsomedial prefrontal cortex (DMPFC), right basal ganglia, frontal lobe (FL), and right hippocampus to create a database for comparisons in BD patients and healthy volunteers. For the present study, we selected the DMPFC as our primary region of interest as it covers brain regions repeatedly shown to be involved in BD (Brady et al., 2012; Davanzo et al., 2001; Schneider et al., 2015; Strawn et al., 2012; Yildiz et al., 2016). The DMPFC voxel dimensions were $2 \times 3 \times 2.5$ cm (15 cm^3) (Fig. 1). Specifically trained, blinded experts at the study site made data acquisitions and metabolite measurements. The investigators at the Brain Imaging Center, McLean Hospital, Belmont, MA accomplished spectral reading and metabolite quantifications also in a blinded fashion.

Unsuppressed water reference spectra were acquired for all acquisitions and used for both eddy current correction and water scaling to estimate absolute metabolite concentrations. The commercial spectral-fitting package LC Model (version 6.1-4E) was used to measure individual metabolite peak integrals (Provencher, 1993). To accept individual metabolite fitting, we set a Cramer-Rao lower bounds threshold of $<20\%$ for NAA, Cho, and tCr and $<40\%$ for Glx and mI, due to the greater difficulty of fitting these metabolites. Of the 136 MR spectra (mania spectra for 48 BD patients, euthymia spectra for 44 BD patients, and control spectra for 44 healthy volunteers) obtained, 9 were excluded due to low spectral resolution. In the present study, metabolite levels were measured in institutional units and expressed as absolute values as well as metabolite/tCr ratios. Sample MR spectra are shown in Fig. 2.

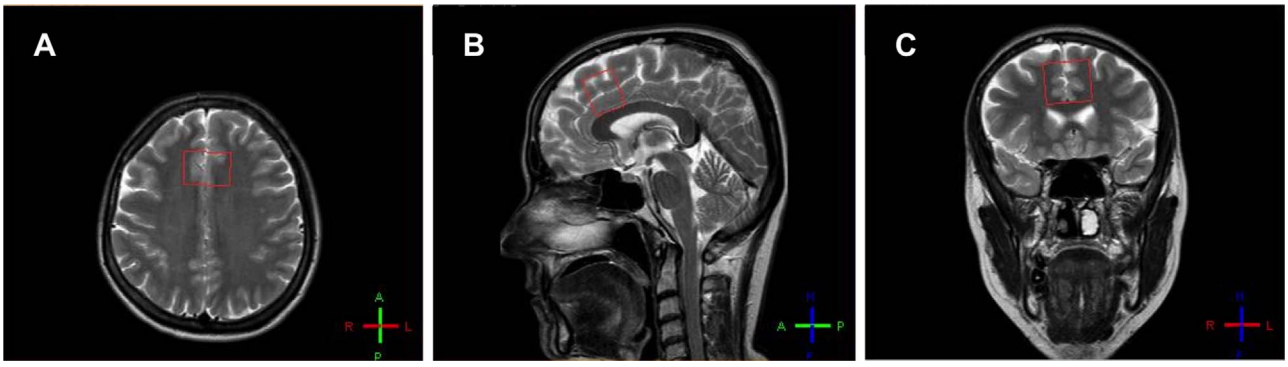

Fig. 1. Voxel placement (2 cm × 3 cm × 2.5 cm) of dorsomedial prefrontal cortex. Axial (A), sagittal (B), and coronal (C) magnetic resonance images.

2.5. Statistical analyses

Demographic and clinical characteristics data were expressed as mean ± SD and analyzed with Student *t*-test, whereas categorical data were expressed with frequencies and analyzed with Pearson χ^2 test. As the data for metabolite levels were nonparametric and the sample sizes were small, data were presented both as mean ± SD and as median and range. Metabolite levels were compared between groups using the Mann-Whitney *U* test (mania vs healthy controls; euthymia vs healthy controls) and the Wilcoxon signed rank test (mania vs euthymia). For BD patients, correlations between the YMRS, CGI-Mania, HAMD-17, and MADRS score changes and metabolite changes (both for absolute values and metabolite/tCr ratios) were explored by Spearman rank correlation. Changes were calculated as [euthymia − mania]. A Bonferroni-corrected two-sided p value < 0.017 was considered statistically significant for multiple metabolite comparisons. All data analysis was performed with IBM SPSS Statistics version 20 (IBM Corporation, Armonk, NewYork) software.

3. Results

Characteristics of BD patients and healthy controls were similar (Table 1). Of the 48 BD patients with baseline clinical and imaging assessments in a manic state, 44 (91.7%) achieved 8 weeks of euthymia and were available for longitudinal assessments (four patients were lost to follow-up). The average duration of time to achieve 8 weeks of euthymia after the end of trial period was 151 ± 104 days.

Absolute metabolite levels and metabolite/tCr ratios in the DMPFC are presented in Table 2. NAA values and NAA/tCr ratio were significantly lower in euthymic BD patients when compared to healthy controls ($p=0.004$ and $p=0.008$, respectively). Other comparisons among groups did not yield significant differences ($p > 0.017$). YMRS, CGI-Mania, HAMD-17, and MADRS score changes did not correlate with metabolite changes ($p > 0.05$).

4. Discussion

In this study, we assessed DMPFC brain metabolites of BD patients in a longitudinal manner in comparison with healthy controls. While we did not find differences in NAA, Cho, tCr, mI, and Glx levels and NAA/tCr, Cho/tCr, mI/tCr, and Glx/tCr ratios during mania vs. euthymia or mania vs. healthy controls, euthymic BD patients had lower NAA values and NAA/tCr ratios compared with healthy volunteers, contrary to our a priori hypothesis.

Previous studies investigating NAA levels and NAA/tCr ratio in FL structures of BD patients and healthy controls yielded variable findings. While some cross-sectional studies involving euthymic BD patients mostly on lithium treatment have reported similar NAA levels and similar or lower NAA/tCr ratio compared with healthy controls in anterior cingular cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and frontal cortex (FC) (Amaral et al., 2006; Brambilla et al., 2005; Hamakawa et al., 1999; Molina et al., 2007), higher NAA/tCr ratio in lithium-treated BD patients has also been found in DLPFC (Brambilla et al., 2005). Euthymic BD patients who were medication free for at least 2 weeks have been found to have lower DLPFC NAA/tCr ratio (Winsberg et al., 2000), whereas manic/mixed patients have been reported to have decreased NAA levels in medial orbital prefrontal cortex and similar NAA levels in DLPFC compared with healthy controls (Cecil et al., 2002; Michael et al., 2003). A recent meta-analysis pooling different BD mood states has found higher NAA levels in DLPFC of BD patients compared to healthy volunteers. The same study has also found similar NAA levels in ACC and FL and NAA/tCr ratio in ACC and DLPFC. Moderate to high inconsistency among these studies investigating metabolite levels has been reported and analyses for mood states could not be performed due to insufficient data (Kraguljac et al., 2012).

Only two studies were identified evaluating hypomanic or manic and euthymic BD states in a longitudinal manner. BD patients who were assessed during hypomania or mania and euthymia have been reported with similar NAA levels or NAA/tCr ratio in FC and/or ACC across mood states using univariate and multivariate analyses when compared with healthy volunteers (Brady et al., 2012; Malhi et al., 2007). Yet one of these studies has reported decreased parietal occipital cortex and ACC lactate concentrations in euthymic patients, implicating a metabolic dysfunction still persistent in euthymia (Brady et al., 2012).

Our results reflect a trait-related abnormality in euthymic BD patients with decreased DMPFC NAA values and NAA/tCr ratio. Trait abnormalities in BD have been extensively reviewed (Ferrier et al., 1999; Kato and Kato, 2000; Langan and McDonald, 2009; Yildiz et al., 2001), supported by several lines of additional evidence. The most prominent findings could be summarized as increased protein kinase A activity, reduced cortical grey matter and cerebral white matter with increased white matter fiber reconstruction (Langan and McDonald, 2009), lower membrane phosphomonoesters (Yildiz et al., 2001), decreased intracellular pH (Kato and Kato, 2000), impaired learning, and cognitive or affective deficits (Ferrier et al., 1999; Langan and McDonald, 2009) in euthymic BD patients. While it is inherently difficult to synthesize these findings into a single theory of trait-related abnormalities of euthymia, mitochondrial dysfunction, abnormalities in brain energy metabolism, and dysregulation in signal transduction have been proposed to explain for the underlying pathophysiology (Kato and Kato, 2000; Stork and Renshaw, 2005; Yildiz et al., 2001). Our findings could fit into these models supporting trait-

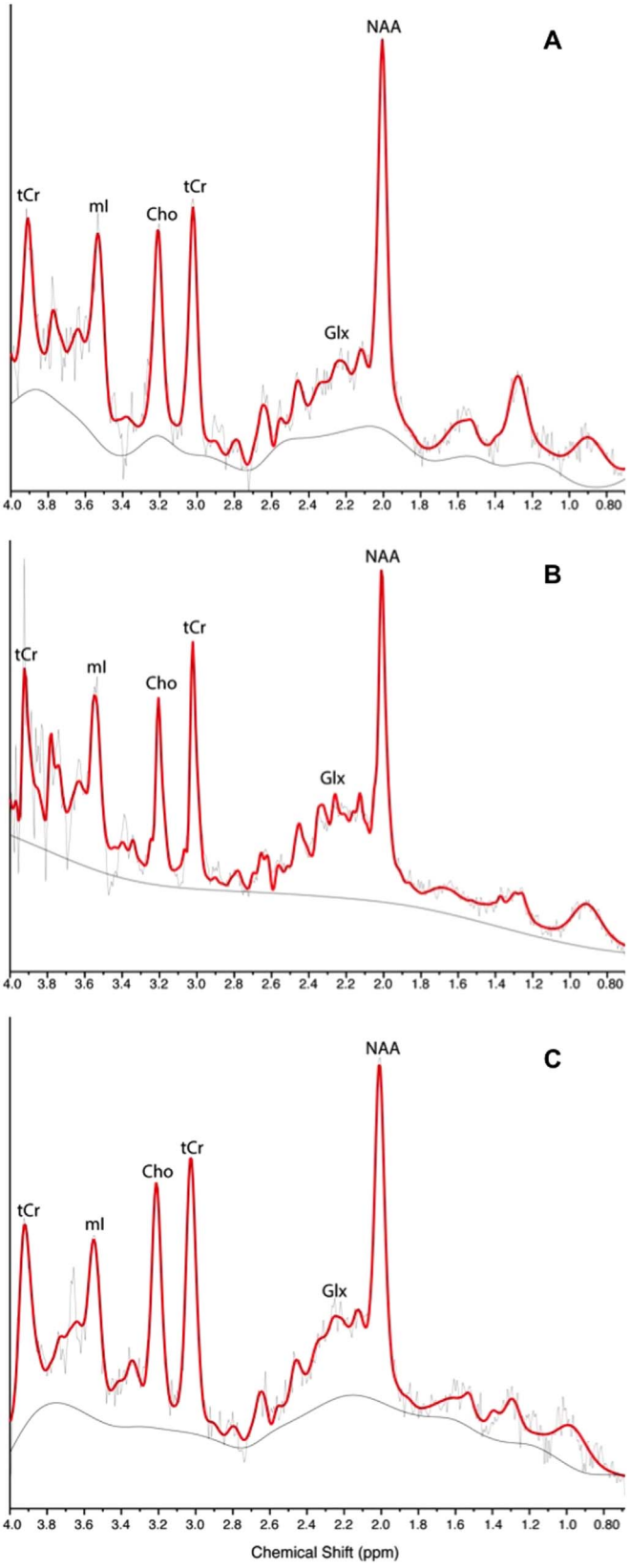

Fig. 2. Sample magnetic resonance spectra of dorsomedial prefrontal. cortex (A) of a healthy volunteer, (B) of a bipolar disorder patient at baseline (mania), and (C) of a bipolar disorder patient in euthymia. Red line indicates modeled spectrum. Chemical shift in parts per million (ppm). Abbreviations: Cho, phosphorylcholine + glycerophosphocholine; tCr, creatine + phosphocreatine; NAA, N-acetylaspartate; mI, myo-inositol; Glx, glutamate + glutamine.

Table 1
Subject characteristics of healthy controls and bipolar disorder (BD) patients.

Characteristic	Healthy controls (n=44)	BD patients (n=48)		*P* value
Age, mean (SD), y	32.0 (12.1)	34.4 (13.2)		0.363[a]
Sex (Female/Male), No.	24/20	24/24		0.663[b]
Handedness (Right/Left), No.	37/7	41/7		0.860[b]
		Mania	**Euthymia[c]**	
YMRS, Mean (SD)	NA	37.8 (5.8)	0.7 (1.4)	
CGI-Mania, Mean (SD)	NA	6.0 (0.9)	1.0 (0.2)	
HAMD-17, Mean (SD)	NA	5.8 (4.0)	0.9 (1.7)	
MADRS, Mean (SD)	NA	6.3 (4.5)	1.3 (1.6)	

Abbreviations: CGI-Mania, Clinical Global Impressions-Bipolar Version Severity of Mania; HAMD-17, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; NA, Not Applicable; YMRS, Young Mania Rating Scale.

[a] For Student's *t*-test.
[b] For Pearson's chi-squared test.
[c] n=44.

related abnormalities in BD as NAA is considered to be a marker of neuronal viability and mitochondrial energy metabolism (Stork and Renshaw, 2005; Zanetti et al., 2015).

Previous MRS studies with variable results present a challenge for interpreting the literature, reflected in moderate to high inconsistency among cross-sectional studies (Kraguljac et al., 2012). Several reasons might be identified as underlying different findings, such as small numbers of patients and controls, a range of BD treatment settings, different durations of mood state prior to MRS assessments, different regions of interest, MR field strengths, and MRS analysis protocols, and mostly cross-sectional study designs (Kraguljac et al., 2012; Yildiz-Yesiloglu and Ankerst, 2006). In line with these differences, limitations of our study include a relatively low (1.5 T) MR field strength, a 'time factor' as healthy controls were scanned only once and a range of duration of time to achieve 8 weeks of euthymia was observed among BD patients, and variable drugs administered to achieve euthymia despite the best efforts to standardize the open fashion treatment. Indeed, it has previously been addressed that possible effects of medications administered before or during euthymia on study endpoints cannot be ruled out (Ferrier et al., 1999; Langan and McDonald, 2009). The possible effects of a time factor are not known as our study was not designed to evaluate metabolite changes over time. Nevertheless, our study was conducted in a longitudinal setting with the largest sample to this date, investigating the state- and trait-related brain metabolite changes in manic and euthymic states. The inclusion of a matching healthy control group aligned with the same MRS procedures and the high portion of BD patients studied both in mania and euthymia contributed to the methodological strength of this study.

In conclusion, we found a trait-related NAA abnormality in euthymic BD patients, relating to previous findings supporting neuronal viability and mitochondrial energy metabolism alterations extending into euthymia. Further studies with longitudinal design and large, homogenous populations are required to better address and clarify the cerebral metabolic alterations which could be related with different mood states and responsible for the etiopathogenesis of BD.

Role of funding sources

This study was supported by the Stanley Medical Research Institute Grant No. 02T-162 (to A. Yildiz), American Psychiatric

Table 2
Metabolite levels in the dorsomedial prefrontal cortex for healthy controls and manic and euthymic bipolar disorder (BD) patients.

	Healthy controls			Manic BD patients			Euthymic BD patients		
	n	Mean ± SD	Median (min;max)	n	Mean ± SD	Median (min;max)	n	Mean ± SD	Median (min;max)
NAA	40	6.41 ± 0.64	6.44 (5.00;7.53)	44	6.19 ± 0.59	6.15 (5.02;7.43)	41	5.96 ± 0.89	6.06 (3.25;8.18)
Cho	39	1.25 ± 0.27	1.23 (0.71;1.77)	41	1.39 ± 0.24	1.40 (1.02;2.15)	41	1.36 ± 0.35	1.35 (0.52;2.43)
tCr	38	4.84 ± 0.67	4.82 (3.37;6.39)	44	4.98 ± 0.68	4.97 (3.58;6.22)	41	4.95 ± 1.08	4.96 (1.94;6.72)
Glx	37	7.35 ± 2.30	7.54 (3.61;11.75)	43	7.96 ± 2.14	7.46 (3.97;12.72)	37	7.59 ± 1.99	7.48 (4.35;11.35)
mI	38	4.66 ± 1.39	4.57 (1.89;7.89)	43	4.63 ± 1.13	4.48 (2.47;7.49)	40	4.60 ± 1.51	4.68 (1.52;7.96)
NAA/tCr	37	1.36 ± 0.22	1.36 (0.96;1.83)	44	1.26 ± 0.18	1.22 (0.95;1.72)	41	1.24 ± 0.21	1.21 (0.90;1.81)
Cho/tCr	36	0.27 ± 0.05	0.25 (0.17;0.43)	40	0.29 ± 0.04	0.29 (0.20;0.38)	41	0.28 ± 0.06	0.26 (0.21;0.46)
Glx/tCr	36	1.55 ± 0.50	1.53 (0.62;2.52)	42	1.62 ± 0.47	1.56 (0.80;3.37)	37	1.49 ± 0.40	1.51 (0.78;2.28)
mI/tCr	36	0.95 ± 0.28	0.93 (0.47;1.86)	42	0.95 ± 0.27	0.94 (0.46;1.72)	40	0.94 ± 0.29	0.92 (0.29;1.67)

Abbreviations: NAA, N-acetylaspartate; tCr, Creatine+phosphocreatine; Cho, Phosphorylcholine+glycerophospocholine; mI, myo-inositol; Glx, glutamate+glutamine.

Association/Astra Zeneca Young Minds in Psychiatry Award (to A. Yildiz), Harvard Medical School Stanley Foundation Bipolar Disorders Research Center, Belmont, Massachusetts (to A. Yildiz), International Sleep Research Foundation, Houston, Texas (to A. Yildiz), and National Institute of Mental Health Grant No. MH58681 (to P.R.). Funding sources had no role in study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Contributors

A. Yildiz, PR, and DO designed the study protocol. A. Yildiz, A. Yurt and NG executed the protocol. BA undertook the statistical analysis. A. Yildiz, PR, and BA contributed to data analysis and interpretation. BA wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors report no biomedical financial interests or potential conflicts of interest related to this study. BA was a researcher in Dokuz Eylul University at the time the study analysis and manuscript preparations were conducted and is now working as a full-time employee in Bristol-Myers Squibb. The research is not connected to the employment of BA with Bristol-Myers Squibb.

Acknowledgments

None.

References

Amaral, J.A., Tamada, R.S., Issler, C.K., Caetano, S.C., Cerri, G.G., de Castro, C.C., Lafer, B., 2006. A 1HMRS study of the anterior cingulate gyrus in euthymic bipolar patients. Hum. Psychopharmacol. 21, 215–220.
Brady Jr., R.O., Cooper, A., Jensen, J.E., Tandon, N., Cohen, B., Renshaw, P., Keshavan, M., Ongur, D., 2012. A longitudinal pilot proton MRS investigation of the manic and euthymic states of bipolar disorder. Transl. Psychiatry 2, e160.
Brambilla, P., Stanley, J.A., Nicoletti, M.A., Sassi, R.B., Mallinger, A.G., Frank, E., Kupfer, D., Keshavan, M.S., Soares, J.C., 2005. 1H magnetic resonance spectroscopy investigation of the dorsolateral prefrontal cortex in bipolar disorder patients. J. Affect. Disord. 86, 61–67.
Brambilla, P., Stanley, J.A., Sassi, R.B., Nicoletti, M.A., Mallinger, A.G., Keshavan, M.S., Soares, J.C., 2004. 1H MRS study of dorsolateral prefrontal cortex in healthy individuals before and after lithium administration. Neuropsychopharmacology 29, 1918–1924.
Cecil, K.M., DelBello, M.P., Morey, R., Strakowski, S.M., 2002. Frontal lobe differences in bipolar disorder as determined by proton MR spectroscopy. Bipolar Disord. 4, 357–365.
Davanzo, P., Thomas, M.A., Yue, K., Oshiro, T., Belin, T., Strober, M., McCracken, J., 2001. Decreased anterior cingulate myo-inositol/creatine spectroscopy resonance with lithium treatment in children with bipolar disorder. Neuropsychopharmacology 24, 359–369.
Ferrier, I.N., Stanton, B.R., Kelly, T.P., Scott, J., 1999. Neuropsychological function in euthymic patients with bipolar disorder. Br. J. Psychiatry 175, 246–251.
Hamakawa, H., Kato, T., Shioiri, T., Inubushi, T., Kato, N., 1999. Quantitative proton magnetic resonance spectroscopy of the bilateral frontal lobes in patients with bipolar disorder. Psychol. Med. 29, 639–644.
Hamilton, M., 1967. Development of a rating scale for primary depressive illness. Br. J. Soc. Clin. Psychol. 6, 278–296.
Kato, T., Kato, N., 2000. Mitochondrial dysfunction in bipolar disorder. Bipolar Disord. 2, 180–190.
Kraguljac, N.V., Reid, M., White, D., Jones, R., den Hollander, J., Lowman, D., Lahti, A. C., 2012. Neurometabolites in schizophrenia and bipolar disorder - a systematic review and meta-analysis. Psychiatry Res. 203, 111–125.
Langan, C., McDonald, C., 2009. Neurobiological trait abnormalities in bipolar disorder. Mol. Psychiatry 14, 833–846.
Malhi, G.S., Ivanovski, B., Wen, W., Lagopoulos, J., Moss, K., Sachdev, P., 2007. Measuring mania metabolites: a longitudinal proton spectroscopy study of hypomania. Acta Psychiatr. Scand. Suppl., 57–66.
Michael, N., Erfurth, A., Ohrmann, P., Gossling, M., Arolt, V., Heindel, W., Pfleiderer, B., 2003. Acute mania is accompanied by elevated glutamate/glutamine levels within the left dorsolateral prefrontal cortex. Psychopharmacology 168, 344–346.
Molina, V., Sanchez, J., Sanz, J., Reig, S., Benito, C., Leal, I., Sarramea, F., Rebolledo, R., Palomo, T., Desco, M., 2007. Dorsolateral prefrontal N-acetyl-aspartate concentration in male patients with chronic schizophrenia and with chronic bipolar disorder. Eur. Psychiatry 22, 505–512.
Montgomery, S., Åsberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.
Moore, G.J., Bebchuk, J.M., Hasanat, K., Chen, G., Seraji-Bozorgzad, N., Wilds, I.B., Faulk, M.W., Koch, S., Glitz, D.A., Jolkovsky, L., Manji, H.K., 2000. Lithium increases N-acetyl-aspartate in the human brain: in vivo evidence in support of bcl-2's neurotrophic effects? Biol. Psychiatry 48, 1–8.
Provencher, S.W., 1993. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Mag. Reson. Med. 30, 672–679.
Schneider, M., Fleck, D., Eliassen, J., Strakowski, S., 2015. Structural and functional magnetic resonance imaging findings and their treatment impact. In: Yildiz, A., Ruiz, C., Nemeroff, C. (Eds.), The Bipolar Book. Oxford University Press, New York, pp. 205–224.
Spearing, M.K., Post, R.M., Leverich, G.S., Brandt, D., Nolen, W., 1997. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res. 73, 159–171.
Stork, C., Renshaw, P.F., 2005. Mitochondrial dysfunction in bipolar disorder: evidence from magnetic resonance spectroscopy research. Mol. Psychiatry 10, 900–919.
Strawn, J.R., Patel, N.C., Chu, W.J., Lee, J.H., Adler, C.M., Kim, M.J., Bryan, H.S., Alfieri, D.C., Welge, J.A., Blom, T.J., Nandagopal, J.J., Strakowski, S.M., DelBello, M.P., 2012. Glutamatergic effects of divalproex in adolescents with mania: a proton magnetic resonance spectroscopy study. J. Am. Acad. Child Adolesc. Psychiatry 51, 642–651.
Winsberg, M.E., Sachs, N., Tate, D.L., Adalsteinsson, E., Spielman, D., Ketter, T.A., 2000. Decreased dorsolateral prefrontal N-acetyl aspartate in bipolar disorder. Biol. Psychiatry 47, 475–481.
Yildiz, A., Aydin, B., Gökmen, N., Yurt, A., Cohen, B., Keskinoglu, P., Öngür, D., Renshaw, P., 2016. Antimanic treatment with tamoxifen affects brain chemistry: a double-blind, placebo-controlled proton magnetic resonance spectroscopy study. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 1, 125–131.
Yildiz, A., Gokmen, N., Kucukguclu, S., Yurt, A., Olson, D., Rouse, E.D., Moore, C., Dicle, O., Renshaw, P.F., 2010. In vivo proton magnetic resonance spectroscopic examination of benzodiazepine action in humans. Psychiatry Res. 184, 162–170.
Yildiz, A., Guleryuz, S., Ankerst, D.P., Ongur, D., Renshaw, P.F., 2008. Protein kinase C inhibition in the treatment of mania. Arch. Gen. Psychiatry 65, 255–263.
Yildiz, A., Sachs, G.S., Dorer, D.J., Renshaw, P.F., 2001. 31P Nuclear magnetic resonance spectroscopy findings in bipolar illness: a meta-analysis. Psychiatry

Res. 106, 181–191.
Yildiz-Yesiloglu, A., Ankerst, D.P., 2006. Neurochemical alterations of the brain in bipolar disorder and their implications for pathophysiology: a systematic review of the in vivo proton magnetic resonance spectroscopy findings. Prog. Neuropsychopharmacol. Biol. Psychiatry 30, 969–995.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435.
Zanetti, M., Loch, A., Machado-Vieira, R., 2015. Translating biomarkers and biomolecular treatments into clinical practice: assessment of hypothesis Driven Clinical Trial Data. In: Yildiz, A., Ruiz, P., Nemeroff, C. (Eds.), The Bipolar Book. Oxford University Press, New York, pp. 149–168.