



Research paper

Neurochemical differences between bipolar disorder type I and II in superior temporal cortices: A proton magnetic resonance spectroscopy study



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ABSTRACT

Background: Despite the diagnostic challenges in categorizing bipolar disorder subtypes, bipolar I and II disorders (BD-I and BD-II respectively) are valid indices for researchers. Subtle neurobiological differences may underlie clinical differences between mood disorder subtypes. The aims of this study were to investigate neurochemical differences between bipolar disorder subtypes.

Methods: Euthymic BD-II patients ($n = 21$) are compared with BD-I ($n = 28$) and healthy comparison subjects (HCs, $n = 30$). Magnetic Resonance Imaging (MRI) and proton spectroscopy (^1H MRS) were performed on a 3T Siemens Tim Trio system. MRS voxels were located in the left/right superior temporal cortices, and spectra acquired with the single voxel Point REsolved Spectroscopy Sequence (PRESS). The spectroscopic data were analyzed with LCModel (Version 6.3.0) software.

Results: There were significant differences between groups in terms of glutamate [$F = 6.27$, $p = 0.003$], glutamate + glutamine [$F = 6.08$, $p = 0.004$], inositol containing compounds (Ino) ($F = 9.25$, $p < 0.001$), NAA [$F = 7.63$, $p = 0.001$] and creatine + phosphocreatine [$F = 11.06$, $p < 0.001$] in the left hemisphere and Ino [$F = 5.65$, $p = 0.005$] in the right hemisphere. Post-hoc comparisons showed that the BD-I disorder group had significantly lower metabolite levels in comparison to the BD-II and the HC groups.

Limitations: This was a cross-sectional study with a small sample size. In addition, patients were on various psychotropic medications, which may have impacted the results.

Conclusions: Neurochemical levels, in the superior temporal cortices, measured with ^1H -MRS discriminated between BD-II and BD-I. Although further studies are needed, one may speculate that the superior temporal cortices (particularly left hemispheric) play a critical role, whose pathology may be related to subtyping bipolar disorder.

1. Introduction

Despite the diagnostic challenges in categorizing bipolar disorder subtypes, bipolar I disorder (BD-I) and bipolar II disorder (BD-II) are valid categorical indices for researchers (Phillips and Kupfer, 2013; Parker and Fletcher, 2014). Along with depressive episodes, presence of manic or hypomanic episodes is the major difference between BD-I and

BD-II disorders. Despite the valid diagnostic boundaries, only limited studies have reported neurobiological differences between the subtypes (Phillips and Kupfer, 2013; Parker and Fletcher, 2014; McGrath et al., 2014).

Genetic studies have identified differences between BD-I and BD-II (Lee et al., 2011; Uemura et al., 2011). Psychosis (Parker and Fletcher, 2014), neurotoxic processes (Yumru et al., 2009; Uemura

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et al., 2011) and cognitive dysfunction (Bora et al., 2011) are more prevalent in BD-I compared to BD-II. Magnetic resonance imaging (MRI) studies have reported that BD-I had more severe findings in comparison to BD-II in volumes (Hauser et al., 2000), white matter lesions (Ambrosi et al., 2013) and functional connectivity (Li et al., 2012). Neurochemistry may also differ between the subtypes.

Proton magnetic resonance spectroscopy ($^1\text{H-MRS}$) can quantify specific neurochemical compounds in the brain *in vivo*. It has been observed in $^1\text{H-MRS}$ that mood state shifts and medications alter metabolites in BD-I (Moore et al., 2007). However, only a few MRS studies have compared BD-I and BD-II. No consistent finding has been reported between the subtypes in the frontal (Winsberg et al., 2000) or temporal (Hamakawa et al., 1998; Atagün et al., 2017) lobes, or the basal ganglia (Silverstone et al., 2004). Only one study detected increased choline concentrations in the basal ganglia in BD-II in comparison to BD-I (Kato et al., 1996).

Patients with bipolar disorder showed fronto-temporal dysconnectivity (Ozerdem et al., 2011) and cortical thinning was specific to superior temporal cortex in BD-I (Hanford et al., 2016). Furthermore, auditory processing deficits in bipolar I disorder are related to left hemisphere superior temporal cortices (McCarley et al., 2008). Moreover, it has been postulated that shared neurochemical abnormalities in superior temporal cortices by schizophrenia and bipolar disorder might be a common feature of psychosis (Nudmamud et al., 2003). On the other hand, superior temporal cortices may have unique local metabolic disturbances in both schizophrenia and bipolar disorder (McNamara et al., 2014). These findings have highlighted the pathology of superior temporal lobes in bipolar disorder. However, it is not clear whether there is difference between subtypes of bipolar disorder.

In this study, we aimed to compare neurochemical differences between BD-I and BD-II disorders utilizing $^1\text{H-MRS}$ in superior temporal cortices. Our hypothesis was that there might be neurochemical differences between the subtypes of bipolar disorder. To our knowledge, this is the first $^1\text{H-MRS}$ study to assess superior temporal lobes in BD-I and BD-II. *In vivo* assessment of metabolite levels in superior temporal lobes may show differences in pathogenesis of the subtypes of bipolar disorder.

2. Methods

All participants provided a written informed consent before study participation. This study was approved by the local Ethical Committee. In a recent article, we have reported abnormal metabolite levels in the superior temporal lobes of participants with BD-I (Atagün et al., 2015). We further enrolled patients with BD-II ($n = 21$, mean age = 38.38 ± 13.84 , 12 women/9 men) and compared with our BD-I sample and healthy comparison subjects (HCs). All patients were euthymic during the study participation. Clinical evaluation tools were Structured Clinical Interview according to the DSM-IV (SCID-I) (First et al., 1996), Young Mania Rating Scale (YMRS) (Young et al., 1978) and Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960).

Data acquisition processes were performed with a 3.0 T Siemens MAGNETOM TIM Trio MR system (Siemens, Erlangen, Germany) and a 32 channel phased-array head coil. T_1 anatomical MRI [MPRAGE sequence, parameters were TE: 3.02, TR: 2000 ms, FOV phase: 100, FOV read: 215, slice thickness: 0.84, number of slices: 192] and spectroscopy voxels [single voxel Point RESolved Spectroscopy Sequence (PRESS); 8 cm^3 voxels ($2 \text{ cm} \times 2 \text{ cm} \times 2 \text{ cm}$); TE: 30 ms, TR: 2000 ms, 128 averages] were recorded to evaluate left and right hemisphere superior temporal lobes which host Heschl's gyrus and planum temporale (Supplementary Fig. 1a). B_0 shimming was manually applied around the voxel. LCModel software (Version 6.3.0) was used to quantify the metabolite levels (Provencher, 2001), using water as internal reference. Representative spectra (Supplementary Fig. 1b) and quantified metabolites are presented in the supplement. Gray matter, white matter and

cerebro-spinal fluid (CSF) contributions to the voxels were analyzed in T_1 weighted structural MRI with Statistical Parametric Mapping-8 (SPM-8) software [Welcome Department of Imaging Neuroscience, London, UK; (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>)] (for further details please see Atagün et al., 2015).

2.1. Statistical analysis

Statistical analyses were performed with SPSS 21 (IBM, Armonk, NY, USA) software. Distribution characteristics of the data are assessed with Kolmogorov–Smirnov and Shapiro–Wilks' Tests. Independent samples *t* Test or Mann–Whitney *U* Tests were performed for two independent group comparisons. Categorical variables were compared with chi-square test. Correlations were examined with Pearson's and Spearman's Correlation Tests. Univariate Analysis of Variance (ANOVA) and Analysis of Covariance (ANCOVA) was performed for three group comparisons for main effects. Chlorpromazine dose equivalents of antipsychotics, age, gender, age at onset, number of episodes, smoking status and alcohol consuming were available variables for covariate analysis. Interaction effects for grey matter, white matter and CSF contributions to the voxels were checked with interaction effect analysis in univariate ANOVA. Kruskal–Wallis Test was used for the comparison of non-Gaussian distributed variables. Post-hoc tests were Bonferroni or Tamhane Tests according to Levene's Homogeneity of Variance Test. Since 6 ANOVAs were performed for 6 metabolites (Glutamate, glutamate + glutamine, inositol containing compounds, creatine + phosphocreatine, choline containing compounds, *n*-Acetyl Aspartate) in the two hemispheres, a Bonferroni correction was applied to the *p* values ($6 \text{ metabolites} \times 2 \text{ hemispheres} = 12$; $0.05/12 = 0.0041$) and level for statistical significance was 0.0041 for metabolite level comparisons. For all other comparisons, cut-off for statistical significance was 0.05.

3. Results

Groups were similar in terms of age, gender, and education (Table 1). Smokers were more frequent in the patient groups [$F = 6.99$, $p = 0.030$] and alcohol consumers were more frequent in the BD-II patient group [$\chi^2 = 9.69$, $p = 0.008$].

Comparison of the metabolite levels revealed that there were significant differences between groups in terms of glutamate [$F = 6.27$, $p = 0.003$], glutamate + glutamine [$F = 6.08$, $p = 0.004$], inositol containing compounds (Ino) [$F = 9.25$, $p < 0.001$], NAA [$F = 7.63$, $p = 0.001$] and creatine + phosphocreatine [$F = 11.06$, $p < 0.001$] in the left hemisphere (Table 2). Post-hoc comparisons showed that the BD-I disorder group had significantly lower metabolite levels in comparison to the BD-II and the HC groups (Table 2). There was no significant difference between the groups in terms of voxel segmentation data (gray/white matter and cerebrospinal fluid content, results are presented in Table 2).

Correlation analysis was performed with Glu, Glx, NAA, Ino, Cr, age, age at onset, duration of the disease, number of episodes, serum lithium levels, serum valproate levels, chlorpromazine equivalent doses of antipsychotics, Young Mania Rating Scale and Hamilton Depression Rating Scale scores variables. There were significant correlations between right hemisphere *N*-Acetyl Aspartate (NAA) levels and age at disease onset ($r^2 = -0.58$, $p = 0.009$), number of hypomanic episodes ($r^2 = -0.51$, $p = 0.032$) in the BD-II group. ANCOVA showed that right hemisphere NAA levels were associated with the YMRS scores [$F = 5.36$, $p = 0.027$], the number of life-time hypomanic episodes [$F = 8.69$, $p = 0.022$], age of disease onset [$F = 5.86$, $p = 0.006$] in the BD-II group. No other significant correlation was observed. Because we presented the BD-I group findings in the past, here we only present correlation analyses within the BD-II group. Medications are presented in Table 3 in the supplement. Metabolite levels did not differ between patients on/off lithium, valproate ($p > 0.05$ for all). There were no

Table 1
Sociodemographic characteristics of the groups.

	BD-I (n = 28)	BD-II (n = 21)	HCs (n = 30)	t/F/ χ^2
Age	35.32 ± 9.12	38.38 ± 13.84	32.90 ± 10.82	1.47
Gender [women (%)]	15 (%53.6)	12 (%57.1)	17 (%56.7)	0.15
Education*	10.89 ± 4.86	12.10 ± 4.09	9.97 ± 3.16	1.66
Age at disease onset*	23.57 ± 8.66	24.71 ± 9.63		−0.44
Duration of the disease**	92.21 ± 107.69	153.43 ± 126.48		−1.83
Total number of				
Episodes	7.82 ± 5.46	8.50 ± 6.87		−0.38
Mania †	2.77 ± 2.18	3.50 ± 3.52		−0.87
Depression	4.22 ± 3.42	4.90 ± 4.15		−0.61
Psychosis during episodes n (%)	18 (%64.3)	8 (%38.1)†		3.31
Nicotine n (%)	18 (%64.3)	14 (%66.7)	10 (%33.3)	6.99
Alcohol n (%)	2 (%7.1)	9 (%40.9)	5 (%16.7)	9.69
YMRS	1.07 ± 1.61	1.48 ± 1.50		−0.90
HAM-D	3.46 ± 3.51	3.38 ± 3.20		0.09

BD-I: Bipolar I disorder, BD-II: Bipolar II disorder, HCs: Healthy controls, *Years, **Months, †Hypomania for patients with bipolar II disorder. YMRS: Young mania rating scale, HAM-D: Hamilton depression rating scale. Bold characters indicate statistical significance. †Psychotic symptoms were observed in depressive episodes of BD-II.

significant differences between psychotic (n = 26) and non-psychotic (n = 23) patients independent of diagnostic subtypes (p > 0.05 for all metabolites in both hemispheres). Psychosis, alcohol or nicotine consumption did not show any significant impact on the metabolite levels (p > 0.05; Supplementary Tables 4 and 5).

4. Discussion

In this study metabolite levels in the superior temporal cortices differed between the BD-I and BD-II groups. The BD-I group had significantly lower metabolite levels in comparison to the BD-II group. Further analysis showed that clinical factors such as psychosis, number of episodes and nicotine or alcohol consumption did not have any impact on metabolite levels. HDRS scores had inverse relationship between NAA and Cr in both right and left hemispheres and Ino and HDRS had correlation in the right hemisphere in BD-I (Atagün et al., 2015). Whereas NAA levels were negatively correlated with age at onset, number of hypomanic episodes and YMRS scores in the BD-II group.

Glutamatergic neurotransmission is maintained by glutamate to glutamine cycle and glial cells serve for the cycle. This cycle is differentially altered in manic and depressive states (Yüksel and Öngür, 2010). Globally Glx is elevated (Dager et al., 2004), however Glu levels are not significantly elevated in bipolar disorder (Yüksel and

Öngür, 2010; Atagün et al., 2015). Since Glx consist of glutamate plus glutamine, elevation of Glx is probably associated with increased glutamine levels. Quantification of glutamine is not possible with low magnetic field scanners, and thus there are not much studies in the literature. Glutamine levels in anterior cingulate cortex were found to be increased in bipolar disorder (Ongur et al., 2008). These findings may indicate that glutamate to glutamine cycle is disturbed in bipolar disorder. There may be a difference in glial physiopathology in BD-I and BD-II.

Inositol levels are found to be changed in bipolar disorder and mood stabilizers alter inositol levels by influencing phospho-inositol cycle (Silverstone and McGrath, 2009). However, the ¹H-MRS literature regarding Ino levels is mixed (Silverstone and McGrath, 2009). Controlling for voxel locations, medications, field strength might be useful in future studies. NAA is a marker of mitochondrial function for oxidative metabolism and neuronal function/viability; decrease of NAA levels indicate neuronal dysfunction (Moffett et al., 2007). Cr metabolites are involved in energy metabolism by transporting high energy phosphorous groups; Cr compounds are highly diffusible and are considered to be stable throughout the brain. However, it has been determined that Cr is not stable in bipolar disorder and schizophrenia (Ongur et al., 2009). Thus, the use of Cr as an internal reference might be erroneous in bipolar disorder and schizophrenia. Correlation analysis revealed

Table 2
¹H-MRS findings.

		BD-I (n = 28)	BD-II (n = 21)	HCs (n = 30)	F	p	Partial η^2	Post-hoc
Right	Glutamate	1.31 ± 0.16	1.46 ± 0.24	1.43 ± 0.18	3.98	0.023	0.11	
	Glx	1.87 ± 0.26	1.98 ± 0.26	1.95 ± 0.26	1.19	0.311	0.04	
	Inositol CC	0.92 ± 0.15	1.02 ± 0.21	1.06 ± 0.09	5.65	0.005	0.25	
	Choline CC	0.29 ± 0.05	0.30 ± 0.05	0.28 ± 0.06	1.04	0.358	0.03	
	NAA	1.59 ± 0.18	1.72 ± 0.18	1.74 ± 0.20	4.94	0.010	0.13	
	Cr	1.12 ± 0.14	1.27 ± 0.19	1.18 ± 0.18	4.38	0.016	0.11	
	Gray matter*	56.83 ± 4.78	57.50 ± 13.89	58.00 ± 4.87	0.14	0.870	<0.01	
	White matter*	28.91 ± 8.09	29.01 ± 5.11	30.58 ± 6.47	0.51	0.604	0.01	
	CSF*	13.58 ± 7.20	13.00 ± 11.72	10.74 ± 5.49	0.93	0.401	0.02	
	Left	Glutamate	0.82 ± 0.11	0.99 ± 0.25	0.95 ± 0.13	6.27	0.003	0.15
Glx		1.11 ± 0.18	1.36 ± 0.37	1.25 ± 0.18	6.08	0.004	0.15	BD-I < HCs, BD-II
Inositol CC		0.57 ± 0.12	0.72 ± 0.17	0.67 ± 0.09	9.25	<0.001	0.21	BD-I < HCs, BD-II
Choline CC		0.17 ± 0.03	0.20 ± 0.04	0.19 ± 0.03	4.18	0.019	0.11	
NAA		1.02 ± 0.13	1.23 ± 0.29	1.17 ± 0.13	7.63	0.001	0.18	BD-I < HCs, BD-II
Cr		0.71 ± 0.11	0.90 ± 0.19	0.81 ± 0.10	11.06	<0.001	0.23	BD-I < HCs, BD-II
Gray matter*		57.03 ± 4.42	57.05 ± 14.84	59.78 ± 5.73	0.85	0.432	0.22	
White matter*		31.06 ± 9.46	30.67 ± 7.77	30.51 ± 6.72	0.04	0.966	<0.01	
CSF*		10.25 ± 7.48	11.85 ± 11.27	9.38 ± 4.56	0.59	0.556	0.02	

All metabolite levels are in institutional units and rounded up (× 1000). Univariate ANOVA, Bonferroni or Tamhane test was picked for post-hoc comparisons. Glx: Glutamate + Glutamine, NAA: N-acetyl-aspartate, Inositol CC: Inositol containing compounds, Choline CC: Choline containing compounds, Cr: Creatine + Phosphocreatine, CSF: Cerebrospinal fluid content. *Voxel segmentation data (percentage), bold indicate statistical significance.

differences between BD-I and BD-II. NAA levels are negatively correlated with number of hypomanic episodes and age at disease onset in BD-II. Whereas in BD-I HDRS scores were negatively correlated with Ino and NAA (reported in Atagün et al., 2015).

Small sample size and being a cross-sectional study are major limitations of this study. Furthermore, patients were on various psychotropic medications and medications are known to alter the metabolites measured by ¹H-MRS (Moore et al., 2000; Moore et al., 2007). Because of its anatomical adjacency to cranium, B₀ and B₁ inhomogeneity are high in temporal lobe (Juchem and de Graaf, 2016). B₀ shimming was performed, however B₁ shimming was not available in this study.

To conclude, levels of metabolites are decreased in BD-I in comparison to BD-II and healthy controls in this study. These findings may indicate that neuronal dysfunction and metabolic decline in the left (dominant) hemisphere superior temporal lobe is specific to BD-I. Although further studies are needed, it can be postulated that pathology of the left hemispheric superior temporal lobe might be more severe in BD-I in comparison to BD-II. Our findings indicate that the left hemispheric superior temporal lobe metabolite levels in BD-I are declined similar to psychotic spectrum disorders rather than BD-II. Further studies comparing manic and hypomanic episodes of BD-I and BD-II may reveal metabolic differences between the subtypes.

Author statement

Contributors

MIA: Prepared the initial study protocol and procedures, data collection, interpretation of the results, wrote the manuscript.

EMS: Data analysis, interpretation of the results and preparation of the manuscript.

SSC: Initial study procedures and data collection.

GKU: Initial study procedures and data collection.

SUK: Initial study procedures and data collection.

AC: Reviewed the protocol, initial study procedures and data collection.

OA: Initial study procedures, data collection and data analysis.

MLP: Scientific supervision during the preparation of the protocol, interpretation of the results and supervision for the manuscript.

CMM: Scientific supervision during the preparation of the protocol, data analysis, interpretation of the results and supervision for the manuscript.

DO: Scientific supervision during the preparation of the protocol, data analysis, interpretation of the results and supervision for the manuscript.

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Conflict of interest

Dr. Kaymak participated in Drsuka's clinical trial (ClinicalTrials.gov Identifier: NCT01129882.), On. Can participated in Janssen Cilag's clinical trial (ClinicalTrials.gov Identifier: NCT02782104). Other authors declare no conflict of interest.

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segmentation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.04.010.

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