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Neurochemical metabolites in the medial prefrontal cortex in bipolar disorder

A proton magnetic resonance spectroscopy study☆

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Abstract

The aim of this study was to investigate proton magnetic resonance spectroscopy metabolite values in the medial prefrontal cortex of individuals with euthymic bipolar disorder. The subjects consisted of 15 patients with euthymic bipolar disorder type I and 15 healthy controls. We performed proton magnetic resonance spectroscopy of the bilateral medial prefrontal cortex and measured levels of N-acetyl aspartate, choline and creatine. Levels of these three metabolites in the medial prefrontal cortex were found to be lower in patients with bipolar disorder compared with healthy controls. A positive correlation was found between illness duration and choline levels in the right medial prefrontal cortex. Our study suggests that during the euthymic period, there are abnormalities in cellular energy and membrane phospholipid metabolism in the medial prefrontal cortex, and that this may impair neuronal activity and integrity.

Key Words

bipolar disorder; proton magnetic resonance spectroscopy; medial prefrontal cortex; N-asetyl aspartate; choline; creatine; degradation; mood disorder; neurochemical metabolite; illness duration; neural regeneration

Research Highlights

(1) N-acetyl aspartate, choline and creatine levels in the medial prefrontal cortex were found to be lower in patients with bipolar disorder compared with healthy controls.
(2) There were no significant differences in N-acetyl aspartate/choline or choline/creatine ratios in the medial prefrontal cortex between patients with bipolar disorder and healthy controls. Illness duration was positively correlated with choline level in the right medial prefrontal cortex.
(3) During the euthymic period, abnormalities in cellular energy metabolism and membrane phospholipid metabolism were present, and this could compromise neuronal activity and integrity in the medial prefrontal cortex.

Abbreviations

^{1}H-MRS, proton magnetic resonance spectroscopy; NAA, N-acetyl aspartate; Cho, choline; Cr, creatine

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INTRODUCTION

Bipolar disorder is a chronic mood disorder characterized by recurrent depressive, manic or mixed attacks. In euthymic period, the patients may return to a normal mood state, or some residual symptoms may remain. Bipolar disorder is cyclical, and it is known that as the number of attacks increases, their duration tends to decrease[1].

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive imaging technique that can measure biochemical structures and metabolites in tissues and present them in a single spectrum. The levels of neurochemical compounds containing N-acetyl aspartate (NAA), choline (Cho) and creatine (Cr) can be determined *in vivo*. NAA is a compound found in adult neurons and is recognized as a marker for neuronal integrity, viability and/or function[2]. Cho resonance reflects levels of phosphocholine, glycerophosphocholine and free choline[3]. It has been suggested that high Cho levels result from changes in cell membrane phospholipid metabolism and membrane degradation[3]. Total Cr, which includes Cr and phosphocreatine, is a marker of energy metabolism. The Cr peak is used as a reference value because it is stable; ^{1}H-MRS is based on the assumption that Cr resonance is constant and is not affected by various pathologies[3].

In bipolar disorder, ^{1}H-MRS studies have reported conflicting results. It has been observed that compared with healthy control groups, the following changes occur in patients with euthymic bipolar disorder: (1) hippocampal NAA levels are reduced, but Cho levels are unaffected[4]; (2) dorsolateral prefrontal cortical NAA/Cr, NAA/Cho and Cho/Cr ratios are decreased[5]; (3) NAA levels have a tendency to decrease in the basal ganglia[6]; and (4) NAA levels are high in the thalamus[7]. Scherk *et al* [8] reported that hippocampal NAA/Cr levels decrease, but the levels in the thalamus and putamen are not different from those of healthy controls. In young patients with bipolar disorder, a study found a decrease in the NAA level in the dorsolateral prefrontal cortex and a link between the number of past affective episodes and Cho levels[9]. It has been reported that during the first episode, bipolar disorder patients show decreased hippocampal NAA/Cr and NAA/Cho ratios, and illness severity and NAA levels show a correlation[10]. However, it has been observed that euthymic bipolar disorder patients do not exhibit changes in neurochemical metabolite levels in different brain regions, such as the anterior cingulate, frontal cortex, dorsolateral prefrontal cortex, parietal cortex, temporal cortex or basal ganglia[11-16].

The medial prefrontal cortex receives mostly dopaminergic and serotonergic projections, mainly from the thalamus, hypothalamus, amygdala, hippocampus, and limbic and medial temporal cortex. It is responsible for emotionally and instinctively organized aspects of behavior[17]. Patients with medial prefrontal cortical damage exhibit dysfunctional social behaviors that involve planning, judgement and decision-making. Inadequate impulse control, euphoria, increased energy, aggression and a tendency toward violence may be observed[18-19]. A decrease in ventromedial prefrontal cortical grey matter volume was detected in bipolar disorder patients with rapid cycling[20]. It is claimed that functional abnormalities may be present in the amygdala and medial prefrontal cortex in patients with euthymic bipolar disorder [21]. However, it was reported that medial prefrontal cortical Cho and Cr levels in patients with bipolar disorder are not different from those of controls[22].

The number of studies that have investigated medial prefrontal cortical neurochemical metabolites in bipolar disorder patients is limited. The aim of this study was to measure NAA, Cho and Cr levels in the medial prefrontal cortex of euthymic bipolar disorder patients.

RESULTS

Sociodemographic and clinical characteristics

Fifteen euthymic bipolar disorder patients and 15 healthy controls were included in the study. Demographic and clinical characteristics are presented in Table 1.

Table 1 Sociodemographic characteristics and clinical features of patients with bipolar disorder and healthy controls

Variable	Bipolar disorder patients (n = 15)	Healthy controls (n = 15)	z	P
Age (year)	38.9±9.3	38.7±8.6	0.062	0.950
Gender (male/female, n)	9/6	9/6		
Education level (year)	9.9±4.5	9.33±3.6	0.462	0.644
Age of illness onset (year)	25.9±7.9	–		
Illness duration (year)	12.5±7.0	–		
Number of attacks	5.6±3.1	–		
Number of hospitalizations	3.4±3.5	–		

Mann-Whitney U test was used to compare the intergroup difference.

There was no significant difference between the groups in age or education level. Six of the patients were on mood-stabilizing drugs and atypical antipsychotics, four were on lithium and atypical antipsychotics, two were taking only lithium, one was taking mood-stabilizing drugs and lithium, one was on mood-stabilizing drugs, and one was using atypical antipsychotics and lithium. All of the patients were in the remission period, and the Hamilton Depression Rating Scale and the Young Mania Rating Scale scores were determined to be zero.

Medial prefrontal cortical NAA, Cho and Cr levels in bipolar disorder patients

In bipolar disorder patients, bilateral medial prefrontal cortical NAA, Cho and Cr levels were found to be lower than in healthy controls (Table 2). No differences were detected in NAA/Cr or Cho/Cr ratios between bipolar disorder patients and healthy controls (Table 2).

Table 2 Comparison of neurochemical metabolites in the medial prefrontal cortex in patients with bipolar disorder *versus* healthy controls

Neurochemical metabolite	Bipolar disorder patients (n = 15)	Healthy controls (n = 15)	z	P
NAA				
Right	7 571±2 850	12 138±2 413	3.609	0.000
Left	6 882±1 734	12 269±2 588	4.334	0.000
Cho				
Right	4 597±2 052	6 921±1 533	3.049	0.002
Left	4 319±1 527	7 290±2 067	3.546	0.000
Cr				
Right	4 173±2 191	6 703±1 775	2.987	0.002
Left	3 718±1 213	6 223±1 325	3.961	0.000
NAA/Cr				
Right	1.82±0.39	1.86±0.29	0.346	0.730
Left	1.98±0.48	2.02±0.39	0.601	0.548
Cho/Cr				
Right	1.12±0.38	1.05±0.18	0.046	0.963
Left	1.21±0.39	1.16±0.19	0.104	0.917

The data are expressed as mean ± SD. Mann-Whitney U test was used to compare the intergroup difference. NAA: N-acetyl aspartate; Cho: choline; Cr: creatine.

A positive correlation was detected between illness duration and right medial prefrontal cortical Cho levels (r_s = 0.605 P = 0.017, Spearman's correlation coefficient). No correlation was detected between illness duration and other neurochemical metabolites (Table 3). No correlation was detected between neurochemical metabolite levels and number of attacks or number of hospitalizations (Table 3). Left medial prefrontal cortical Cr values were found to be significantly lower in patients who used lithium (n = 8) compared with those who did not (n = 7) (z = 2.459, P = 0.014, Mann-Whitney U test). There was no difference in other metabolite levels between bipolar disorder patients who used lithium and those who did not (right medial prefrontal cortical NAA, Cho, Cr, NAA/Cr, Cho/Cr: z = 1.389, 0.985, 0.521, 1.143, 0.571, respectively; left medial prefrontal cortical NAA, Cho, NAA/Cr, Cho/Cr: z = 0.463, 1.389, 0.232, 1.504, respectively; P > 0.05 for all, Mann-Whitney U test).

Table 3 Correlation between neurochemical metabolites in the medial prefrontal cortex in patients with bipolar disorder and duration of illness, as well as number of attacks and number of hospitalizations

Variable	Neurochemical metabolite	r_s	P
Duration of illness			
Right mPFC	Cho	0.605	0.017
	Cr	0.464	0.081
	NAA	0.436	0.104
	Cho/Cr	0.139	0.652
	NAA/Cr	0.055	0.857
Left mPFC	Cho	0.431	0.109
	Cr	0.108	0.701
	NAA	0.413	0.126
	NAA/Cr	0.233	0.404
	Cho/Cr	0.445	0.096
Number of attacks			
Right mPFC	Cho	0.367	0.179
	Cr	0.207	0.459
	NAA	0.055	0.847
	Cho/Cr	0.051	0.870
	NAA/Cr	0.337	0.260
Left mPFC	Cho	0.120	0.669
	Cr	0.024	0.933
	NAA	0.231	0.407
	NAA/Cr	0.004	0.990
	Cho/Cr	0.078	0.781
Number of hospitalizations			
Right mPFC	Cho	0.054	0.847
	Cr	0.036	0.898
	NAA	0.013	0.962
	Cho/Cr	0.057	0.854
	NAA/Cr	0.149	0.627
Left mPFC	Cho	0.101	0.720
	Cr	0.170	0.545
	NAA	0.197	0.482
	NAA/Cr	0.227	0.415
	Cho/Cr	0.290	0.294

Spearman's correlation analysis was used. mPFC: Medial prefrontal cortex; Cho: choline; Cr: creatine; NAA: N-acetyl aspartate.

DISCUSSION

Middle-aged patients with a diagnosis of bipolar disorder type I who regularly used psychotropic drugs participated in the study. Medial prefrontal cortical NAA, Cho and Cr levels were found to be lower in patients with euthymic bipolar disorder compared with healthy controls. In bipolar disorder, it has been reported that NAA, NAA/Cr and NAA/Cho are decreased in the frontal cortex and dorsolateral prefrontal cortex[5, 23]. Similarly, studies have shown reduced prefrontal NAA levels in children with bipolar disorder[9, 24]. It was reported that Cho and Cr

levels are decreased in the frontal cortex, basal ganglia and hippocampus in bipolar disorder[4, 13, 25]. Frey *et al* [26] determined that dorsolateral prefrontal cortical Cr levels were low in unmedicated patients with bipolar disorder. It has been proposed that cellular energy and phospholipid metabolism are impaired in bipolar disorder patients, and that mitochondrial dysfunction occurs. However, some studies reported conflicting results for the same or different brain regions. A number of studies found increased levels of Cho and Cr in the basal ganglia, hippocampus, orbitofrontal cortex and thalamus in bipolar disorder patients[7, 27-28]. Furthermore, some studies found no significant changes in neurochemical metabolite levels in the prefrontal cortex, basal ganglia or hippocampus in bipolar disorder [14, 16, 29-30]. Normal neurochemical metabolite levels reflect healthy neuronal function. Our results suggest impaired neuronal viability and integrity, as well as abnormalities in membrane phospholipid and energy metabolism in the medial prefrontal cortex of patients with euthymic bipolar disorder.

The medial prefrontal cortex plays a pivotal role in the regulation of emotion and social functioning. There are a limited number of studies investigating neurochemical metabolites in this brain region. One study found that neurochemical metabolite levels, including those of Cho, Cr, myo-inositol and NAA, in the medial prefrontal cortex are similar in unaffected and affected participants at high genetic risk for bipolar disorder and in control participants[31]. The conflicting results in this field and the limited number of studies make our findings difficult to comment on. The patients in our study were followed and treated regularly. In our study, none of the patients exhibited manic or depressive symptoms. However, we did not clinically evaluate medial prefrontal cortical functions, such as social function. Further study is required to assess social function in more details. Studies of bipolar disorder that investigate pathophysiology and neurochemistry are increasing in number. However, interpreting results is challenging because the illness includes depressive, manic and euthymic periods, and different brain regions regulate mood. It has been reported that the NAA level in the frontal cortex is low during manic episodes[32], but that NAA, Cho and Cr levels in the dorsolateral prefrontal cortex of bipolar disorder patients are similar to that in controls[33]. Some researchers evaluate bipolar disorder patients in euthymic, depressive and manic episodes together[16, 34-37], and some studies include bipolar disorder type I and type II patients[16, 28, 35-36]. Clearly, there is a need for investigators to standardize the use of patient groups to facilitate the comparison of results.

We detected a positive correlation between illness duration and Cho levels in our study; as illness duration increased, Cho levels rose. It was reported that there is a relationship between Cho levels and the number of affective episodes[9]. However, Gallelli *et al* [38] reported that NAA/Cr levels are not related to age, illness duration, or lithium and valproate usage. Supposedly, NAA/Cr level is not a marker for bipolar disorder. DelBello *et al* [39] investigated the effects of olanzapine treatment on medial and lateral prefrontal neurochemical metabolite levels in patients who had their first manic attack. A significant increase was observed in the prefrontal NAA levels of patients who responded to olanzapine. An increase in medial and lateral prefrontal Cho levels was observed 1 week after olanzapine treatment. It was found that in manic patients successfully treated with olanzapine, prefrontal cortical neuronal activity and functioning tended to increase. The increase in Cho levels with treatment was interpreted as an amelioration of abnormalities in cell membrane metabolism or secondary messenger pathways. In our study, the patients were in the euthymic state, and they were taking mood-regulating drugs and/or atypical antipsychotics and antidepressants. However, medial prefrontal cortical neurochemical metabolite levels were found to be lower than in controls. Our study supports the hypothesis that illness duration and Cho levels are related. As illness duration increases, so do abnormalities in membrane phospholipid metabolism.

A limitation of our study is the small number of patients. The other limitation in our study is that all participants used psychotropic drugs, particularly atypical antipsychotic and mood-regulating drugs, and these drugs are likely to have caused neurochemical changes in the brain. In our study, left medial prefrontal cortical Cr values were found to be significantly lower in patients who used lithium compared with those who did not. No differences were detected in other neurochemical metabolites. However, the small number of patients and their use of multiple drugs might have affected our results. It has been reported that lithium affects neurochemical metabolite levels, has neuroprotective and neurotrophic properties, and increases mitochondrial functioning[16, 40-41]. However, another study failed to establish a relationship between lithium treatment and neurochemical metabolite levels[8]. There are conflicting results on valproate usage; while it has been claimed that valproate positively affects neurochemical metabolite levels and has neuroprotective effects[42], others have found that the drug does not affect neurochemical metabolites[14].

Despite the conflicting evidence, it is highly probable that psychotropic drugs affect neurochemical metabolites. It is very difficult to find bipolar disorder patients who do not use medications. More studies are required to clarify the effects of drugs on neurochemical metabolites.

Yildiz-Yesiloglu and Ankerst[2] reviewed studies performed in this field between 1978 and 2005. They determined that during euthymic periods, NAA levels in bipolar disorder patients are low in frontal structures and the hippocampus, and that lithium increases NAA levels. Although Cho changes were also reported, the findings were not consistent. It is thought that neurochemical changes in fronto-limbic-subcortical circuits may play a role in the pathophysiology of bipolar disorder. There are also putative abnormalities in cell membrane phospholipid metabolism, cell energy metabolism, and myelin production/maintenance in the frontal cortex, cingulate cortex, hippocampus and basal ganglia. We previously reported that dorsolateral prefrontal cortical NAA levels in bipolar disorder, schizoaffective disorder and schizophrenia patients were low compared with healthy controls. However, decreased Cho and Cr levels were only detected in bipolar disorder and schizoaffective disorder, and it was concluded that this result could be because of the affective properties of both illnesses[43].

In our study, medial prefrontal cortical NAA, Cho and Cr levels were found to be lower in bipolar disorder patients compared with healthy controls, but no differences were detected in NAA/Cr or NAA/Cho levels. Our results suggest that in euthymic bipolar disorder patients, there are neurochemical abnormalities in the medial prefrontal cortex, impairing neuronal activity and integrity, and that there are abnormalities in cellular energy and membrane phospholipid metabolism. Our findings need confirmation in a larger patient population and long-term studies. Studies directed at the relationship between these neurochemical changes and mood symptoms, social behavior and functionality are needed.

SUBJECTS AND METHODS

Design

A case-control study.

Time and setting

This study was performed in the Department of Psychiatry, Faculty of Medicine, Pamukkale University, Turkey between May 2008 and May 2009.

Subjects

Fifteen healthy controls and 15 patients who were diagnosed with type I bipolar disorder according to the *Diagnostic and Statistical Mental Disorders Manual, Fourth Edition* [1] were included in the study. Patients with bipolar disorder, 18–60 years old, who had not had a mood episode in the preceding 3 months, were informed about the study. The control group was composed of physically and mentally healthy individuals whose age and gender were similar to those of the patient group. Members of the control group were invited to participate *via* announcements on the bulletin boards of the hospital. After being informed about the purpose of the study and after undergoing psychiatric evaluation, patients and healthy volunteers were included in the study. The study was performed in accordance with the *Declaration of Helsinki* [44].

Exclusion criteria for patients with bipolar disorder and healthy controls: (1) mental retardation; (2) alcohol or substance use; (3) electroconvulsive therapy in the previous 6 months; (4) presence of neurological or organic mental disorder.

Methods

Collection of clinical data

We prepared a data form that contained sociodemographic data and information about the clinical features of the illness and applied it to the study participants. The Hamilton Depression Rating Scale[45-46] and the Young Mania Rating Scale[47-48] were applied to bipolar disorder patients. Patients and controls underwent a bilateral ^{1}H-MRS scan of the medial prefrontal cortex region.

^{1}H-MRS

^{1}H-MRS scans were performed with a 1.5-Tesla magnetic resonance instrument (GE Medical Systems, Milwaukee, WI, USA) using a standard head coil. The magnetic resonance protocol employed a T2-weighted fast spin echo sequence with 10-mm-thickness of the coronal plane using repetition time/echo time = 3 000/85; field of view = 14; matrix = 352 × 352. Single voxel (^{1}H-voxel) magnetic resonance spectroscopy was used to analyze the bilateral medial prefrontal cortex region (Figures 1 and 2).

The volume of interest being analyzed was manually and visually placed in the relevant regions to ensure that it covered the relevant frontal lobe areas. The chemical-shift-selective pulse technique[49] was used to suppress signals originating from water.

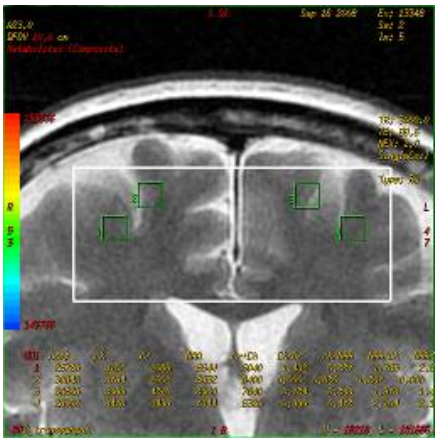

Figure 1 Application of single voxel magnetic resonance spectroscopy in the medial prefrontal region in a patient with bipolar disorder.

The outlined frame 2 indicates the right medial prefrontal cortex and corresponding neurochemical metabolite values; the outlined frame 3 indicates the left medial prefrontal cortex and corresponding neurochemical metabolite values.

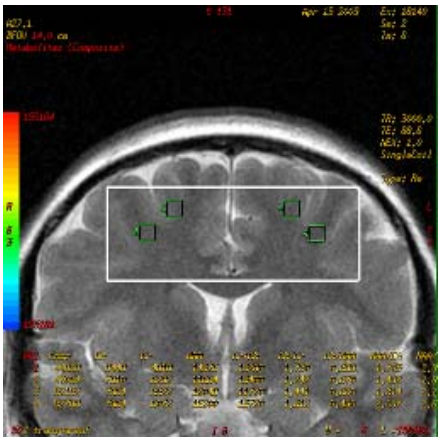

Figure 2 Application of single voxel magnetic resonance spectroscopy in the medial prefrontal cortex in a healthy control subject.

The outlined frame 2 indicates the right medial prefrontal cortex and corresponding neurochemical metabolite values; the outlined frame 3 indicates the left medial prefrontal cortex and corresponding neurochemical metabolite values.

Subsequently, we employed the point-resolved spectroscopy technique[50], which localizes spectroscopy volume (repetition time/echo time = 3 000/14 and 35). As a result, short and medium duration repetition time spectra were obtained inside the volume of interest in both medial prefrontal cortex regions, and these data were evaluated using GE spectral analysis software. Values for NAA/Cr and Cho/Cr were calculated from the obtained metabolite values.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (Statistical Packages for the Social Sciences, Chicago, IL, USA). Conformity of the variables to normal distribution was assessed with the Kolmogorov-Smirnov goodness-of-fit test. Because of the small number of subjects, the variables were not normally distributed, and nonparametric statistical techniques were used. Differences between measurable values between groups were analyzed using the Mann-Whitney *U* test. Relationships between neurochemical metabolite levels and illness duration and the number of attacks were evaluated using Spearman's rank-order correlation.

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Author contributions: Osman Özdel, Demet Kalayci, Gülfizar Sözeri-Varma, Yilmaz Kiroğlu, and Tuğçe Toker-Uğurlu were responsible for data collection and analysis. Osman Özdel, Demet Kalaycı, and Yilmaz Kiroğlu were in charge of the study concept/design and guidance. Osman Özdel, Demet Kalayci, Gülfizar Sözeri-Varma, Selim Tümkaya, and Tuğçe Toker-Uğurlu participated in statistical analysis and wrote the manuscript. All authors approved the final manuscript.

Conflicts of interest: None declared.

Ethical approval: Approval was obtained from the local ethics committee of Pamukkale University.

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