

Research report

# <sup>1</sup>H magnetic resonance spectroscopy investigation of the dorsolateral prefrontal cortex in bipolar disorder patients

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## Abstract

**Background:** Magnetic resonance spectroscopy studies (MRS) reported abnormally low levels of *N*-acetylaspartate (NAA, a marker of neuronal integrity) in dorsolateral prefrontal cortex (DLPFC) of adult bipolar patients, suggesting possible neuronal dysfunction. Furthermore, recent MRS reports suggested possible lithium-induced increase in NAA levels in bipolar patients. We examined with in vivo <sup>1</sup>H MRS NAA levels in the DLPFC of adult bipolar patients.

**Methods:** Ten DSM-IV bipolar disorder patients (6 lithium-treated, 4 drug-free) and 32 healthy controls underwent a short echo-time <sup>1</sup>H MRS session, which localized an 8 cm<sup>3</sup> single-voxel in the left DLPFC using a STEAM sequence.

**Results:** No significant differences between the two groups were found for NAA, choline-containing molecules (GPC+PC), or phosphocreatine plus creatine (PCr+Cr) (Student *t*-test, *p*>0.05). Nonetheless, NAA/PCr+Cr ratios were significantly increased in lithium-treated bipolar subjects compared to unmedicated patients and healthy controls (Mann–Whitney *U*-test, *p*<0.05).

**Limitations:** Relatively small sample size may have reduced the statistical power of our analyses and the utilization of a single-voxel approach did not allow for the examination of other cortical brain areas.

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**Conclusions:** This study did not find abnormally reduced levels of NAA in left DLPFC of adult bipolar patients, in a sample of patients who were mostly on medications. However, elevated NAA/PCr+Cr ratios were shown in lithium-treated bipolar patients. Longitudinal  $^1\text{H}$  MRS studies should further examine NAA levels in prefrontal cortex regions in untreated bipolar patients before and after mood stabilizing treatment.

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**Keywords:** Neuroimaging; Affective disorder; Mood disorder; NAA; Lithium

## 1. Introduction

$^1\text{H}$  magnetic resonance spectroscopy (MRS) represents a non-invasive tool for in vivo studies of the brain levels of important neurochemicals, such as *N*-acetylaspartate (NAA), myo-inositol (INO), phosphocreatine plus creatine (PCr+Cr), and choline-containing molecules (GPC+PC, glycerophosphocholine plus phosphocholine) (Soares et al., 1996; Stanley et al., 2000; Stanley, 2002). In particular, NAA is exclusively found in neurons and therefore thought to be a marker of neuronal integrity, viability, and function (Urenjak et al., 1993).

A  $^1\text{H}$  MRS study showed significant reductions of NAA peaks in the DLPFC of adult bipolar disorder subjects (Winsberg et al., 2000), whereas two other MRS studies did not find any differences in DLPFC (Bertolino et al., 2003) or frontal lobes (Hamakawa et al., 1999). The levels of INO, GPC+PC, or PCr+Cr did not differ significantly between bipolar patients and healthy controls in these studies. Chang et al. (2003) reported reduced NAA levels in DLPFC in a sample of pediatric bipolar patients who had a parent with bipolar disorder. Furthermore, there is extensive literature from functional imaging and postmortem studies in support of DLPFC dysfunction in bipolar disorder (Rajkowska et al., 2001; Rajkowska, 2002; Soares, 2003). Thus, the investigation of the NAA resonance in the DLPFC of bipolar disorder patients is of great interest for studies of illness pathophysiology (Stanley, 2002; Soares, 2003).

Interestingly, a  $^1\text{H}$  MRS study reported increased levels of total brain NAA (i.e. combining concentrations from four different voxel placements, right frontal, left temporal, central occipital, and left parietal lobes) in a mixed group of bipolar and healthy subjects after 4 weeks of lithium treatment (Moore et al., 2000a). Also, significantly increased levels of NAA/PCr+Cr ratios have been found in

lithium-treated bipolar patients compared to healthy controls in temporal lobes (Silverstone et al., 2003) and basal ganglia (Sharma et al., 1992). Consistently, controlled MRI studies showed increased total brain gray matter volumes in bipolar patients after lithium treatment (Moore et al., 2000b; Sassi et al., 2002). These effects could possibly result from the neuroprotective actions of lithium treatment, probably as a result of increased levels of cytoprotective proteins (i.e. bcl-2) and neurotrophins (i.e. nerve growth factor), and by decreased levels of some pro-apoptotic proteins (i.e. p53, Bax) (Chen and Chuang, 1999; Hellweg et al., 2002; Manji et al., 2000).

In the present study, we examined the levels of NAA in DLPFC of adult bipolar patients with  $^1\text{H}$  MRS to examine the hypothesis of neuronal dysfunction in this brain region. Furthermore, we also examined possible effects of lithium treatment.

## 2. Methods

### 2.1. Subjects

Ten bipolar disorder outpatients (mean age  $\pm$  S.D.=36.6 $\pm$ 13.9 years; 8 females, 2 males; 1 depressed, 9 euthymic; 8 type-I, 2 type-II) as diagnosed by the Structured Clinical Interview for DSM IV, SCID (Spitzer et al., 1994) were recruited. Four bipolar patients were off all psychotropic drugs for at least 2 weeks and off lithium for at least 1 month (mean age  $\pm$  S.D.=39.0 $\pm$ 12.8 years; 3 females, 1 male), whereas 6 bipolar patients were on lithium monotherapy at the time of participation in the study (mean age  $\pm$  S.D.=35.0 $\pm$ 15.5 years; 5 females, 1 male). Bipolar individuals had no axis I comorbid psychiatric disorders, current medical problems, or alcohol/substance abuse within the 6 months preceding the study. Thirty-two healthy controls (mean

age $\pm$ S.D.=34.8 $\pm$ 9.9 years; 16 females, 16 males) with no DSM-IV axis I disorders, as determined by the SCID-IV, non-patient version, and without any current medical problems, current or prior history of substance abuse/dependence or any psychiatric disorders in self or in first-degree relatives were studied. All subjects provided signed informed consent, after having understood all issues involved in participation in the study protocol. This research study was approved by the local biomedical IRB.

## 2.2. $^1\text{H}$ MRI/MRS procedure

In vivo  $^1\text{H}$  MRS was conducted on a 1.5 T GE Signa Imaging System (General Electric Medical Systems, Milwaukee, WI). A set of sagittal and coronal scout images was first obtained to verify patient position, image quality, position the voxel and locate a midline sagittal image. Forty-five to 56 sagittal slices covering

the entire brain were obtained using a fast spin echo (FSE) sequence (TR=25 ms, TE=17 ms, flip angle=40°, FOV=24 cm, slice thickness=3 mm, NEX=1, matrix size=256 $\times$ 128) for tissue segmentation analysis of the  $^1\text{H}$  spectroscopy voxels. The MRS data was collected with a STEAM sequence (TE=20 ms, TM=13.6 ms, TR=1.5 s, bandwidth=2 kHz, 2048 complex data points, 300 acquisitions, voxel dimension 2.0 $\times$ 2.0 $\times$ 2.0 cm<sup>3</sup>). This 8 cm<sup>3</sup> voxel was placed in the left DLPFC, which was identified on a set of sagittal and coronal images (Fig. 1). Water unsuppressed spectra were also collected for absolute quantification (16 acquisitions). The position of the voxel was visually inspected and adjusted based on identifiable anatomical landmarks in reference to standard brain atlases (Jackson and Duncan, 1996; Yuh et al., 1994). The superior frontal sulcus, the lateral fissure, and the genu of the corpus callosum were used as anatomical boundaries for the voxel placement.

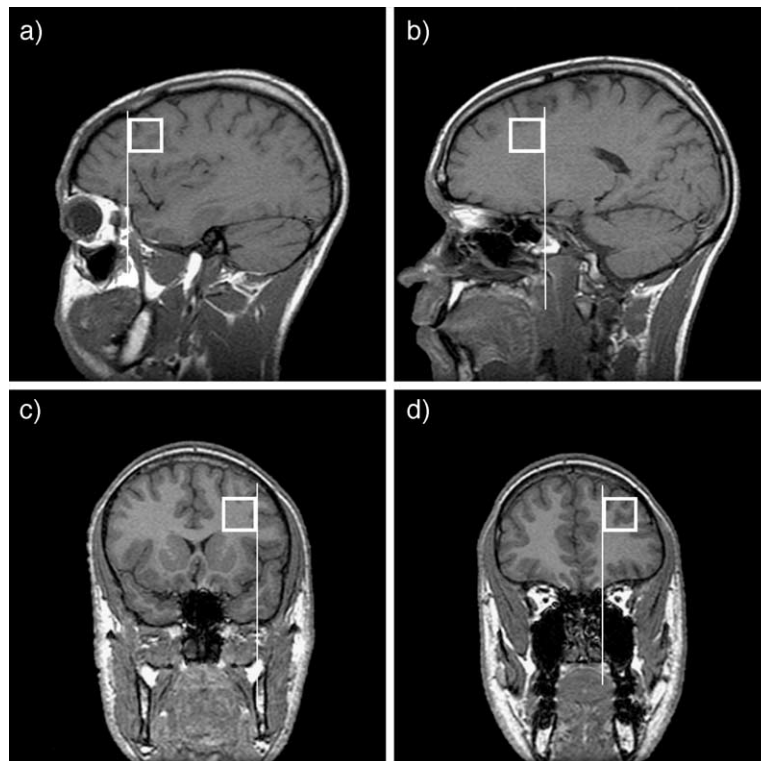


Fig. 1.  $^1\text{H}$  MRS volume of interest in left dorso-lateral prefrontal cortex. The white box represents the location of the volume of interest (2 $\times$ 2 $\times$ 2 cm<sup>3</sup>) in the left dorsolateral prefrontal cortex (DLPFC). The thin lines in pictures (a) and (b) represent the position of the coronal images in (c) and (d), whereas the thin lines in (c) and (d) represent the position of the sagittal images in (a) and (b). The superior frontal sulcus, the lateral fissure, and the genu of the corpus callosum were used as anatomical boundaries for the voxel placement.

The post-processing and quantification steps for the short TE STEAM MRS data were 100% automated. The unsuppressed water spectrum was used to correct for any eddy current effects. No apodization was applied and any residual water signal was removed by using the operator independent SVD-based method (Stanley et al., 2002). Five Gaussian damped sinusoids were used to model the in vivo data in the time domain using the Marquardt algorithm [NAA at 2.01 ppm; PCr+Cr at 3.02, 3.93 ppm; GPC+PC at 3.21 ppm; INO at 3.54 ppm]. To ensure that the signals of overlapping and of lesser amplitudes (i.e. metabolites with multiplet structures and macromolecules) have negligible influence on the fitting of the singlets, the first 37 ms of the free-induction decay (FID) signal were omitted in the fitting, which has been shown to reliably and accurately quantify NAA, PCr+Cr and GPC+PC. The unsuppressed water signal, along with the appropriate correction factors, was applied to obtain absolute quantification values with units of mmol/kg wet weight.

### 2.3. Statistical analyses

Analyses were performed using the SPSS for Windows software, version 11.0 (SPSS, Chicago), and the level of significance was set at  $p < 0.05$  (two-tailed).

## 3. Results

Bipolar patients did not differ significantly for metabolite levels or voxel composition in left DLPFC compared to healthy controls (ANCOVA, age and gender as covariates,  $p > 0.05$ ) (Table 1). No significant differences were found between bipolar patients and age- and gender-matched healthy controls ( $N=10$ ; mean age  $\pm$  S.D. =  $35.5 \pm 11.8$  years; 2 females, 8 males) ( $t$ -Student test,  $p > 0.05$ ) or between bipolar and control female subjects (ANCOVA, age as covariate,  $p > 0.05$ ). However, lithium-treated bipolar individuals had significantly higher levels of NAA/PCr+Cr compared to drug-free bipolar patients (mean  $\pm$  S.D. =  $1.54 \pm 0.15$  vs.  $1.22 \pm 0.22$  mmol/kg wet weight;  $Z = -2.35$ ,  $p = 0.02$ ) and healthy controls ( $Z = -2.38$ ,  $p = 0.02$ ) (Fig. 2). No significant differences were found between lithium-

Table 1

<sup>1</sup>H MRS metabolite measures and voxel composition for left dorsolateral prefrontal cortex in bipolar patients and matched healthy subjects

	Bipolar patients ( $N=10$ )	Healthy controls ( $N=32$ )	ANCOVA	
			$f$	$p$
NAA	$8.36 \pm 0.60$	$7.98 \pm 0.86$	1.71	0.20
PCr+Cr	$6.44 \pm 1.14$	$6.23 \pm 0.73$	0.23	0.64
GPC+PC	$1.07 \pm 0.38$	$1.10 \pm 0.30$	0.03	0.87
NAA/PCr+Cr	$1.41 \pm 0.24$	$1.36 \pm 0.17$	1.01	0.32
NAA/GPC+PC	$2.99 \pm 1.46$	$2.67 \pm 0.80$	0.68	0.42
GPC+PC/PCr+Cr	$0.55 \pm 0.20$	$0.55 \pm 0.16$	0.04	0.85
Gray matter (ml)	$3.16 \pm 0.99$	$3.07 \pm 0.75$	0.26	0.61
White matter (ml)	$4.36 \pm 1.04$	$4.45 \pm 0.81$	0.22	0.64
CSF (ml)	$0.13 \pm 0.11$	$0.14 \pm 0.14$	0.18	0.67

NAA=*N*-acetyl-aspartate, PCr+Cr=phosphocreatine plus creatine, GPC+PC=choline-containing molecules. Absolute values are expressed as mmol/kg wet weight.

treated and unmedicated bipolar patients for socio-demographic (i.e. age, gender, educational level) and clinical variables (age at onset, length of illness, prior number of affective episodes, episode type, bipolar disorder sub-type) ( $t$ -Student test or Chi-square test,  $p > 0.05$ ).

Age was directly correlated with GPC+PC, but not with any other metabolite, in healthy controls ( $r = 0.54$ ,  $p < 0.01$ ), but not in bipolar patients ( $r = 0.18$ ,  $p = 0.65$ ). Clinical variables (i.e. length of illness, mean  $\pm$  S.D. =  $15.9 \pm 10.3$  years, median: 14.0; age at onset, mean  $\pm$  S.D. =  $19.5 \pm 6.2$  years, median: 20.0; prior affective episodes, mean  $\pm$  S.D. =  $24.1 \pm 34.5$ , median: 8.0; weeks on lithium, mean  $\pm$  S.D. =  $240.3 \pm 386.3$  weeks, median: 85.0; lithium dose, mean  $\pm$  S.D. =  $1162.5 \pm 501.4$  mg/day, median = 1050.0) did not significantly correlate with any measured metabolites (Spearman correlation coefficients,  $p > 0.05$ ), except for GPC+PC and NAA/GPC+PC, which significantly correlated with number of prior affective episodes (Spearman's  $\rho = 0.82$ ,  $p = 0.02$ ; Spearman's  $\rho = -0.79$ ,  $p = 0.02$ , respectively).

## 4. Discussion

In this study, no significant differences for left DLPFC NAA concentrations were found between bipolar patients and healthy individuals. Winsberg et al. (2000) previously reported abnormally low NAA/

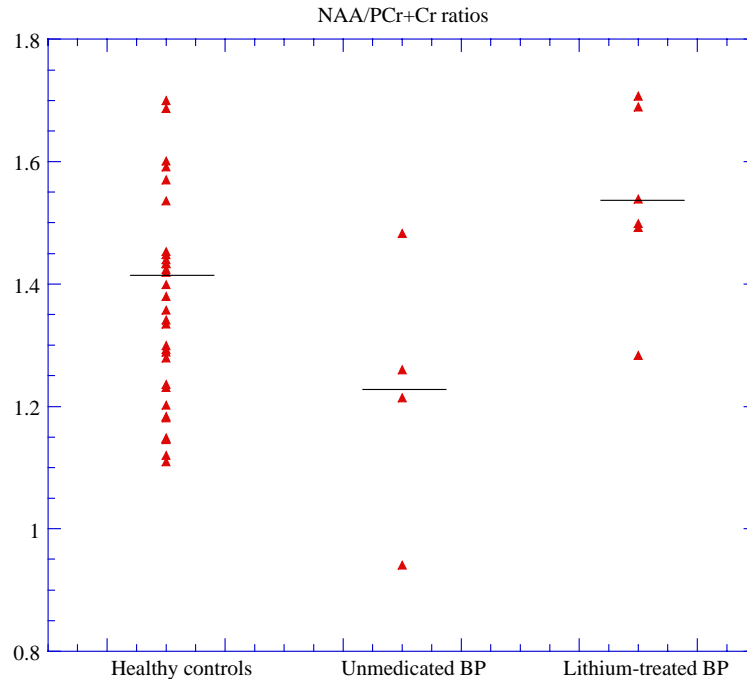


Fig. 2. NAA ratios to PCr+Cr in the left dorsolateral prefrontal cortex of healthy subjects and unmedicated and lithium-treated bipolar individuals. Lithium-treated bipolar patients (BP) had significantly higher levels of NAA/PCr+Cr compared to drug-free BP ( $Z=-2.35$ ,  $p=0.02$ ) and healthy controls (HC) ( $Z=-2.38$ ,  $p=0.02$ ).

PCr+Cr ratios in DLPFC in adult bipolar patients, while a second report did not find abnormalities in NAA levels in this same brain region (Bertolino et al., 2003). Furthermore, another MRS study did not find abnormalities in NAA levels in the frontal lobes of bipolar patients (Hamakawa et al., 1999). The discrepancy in these findings may reflect differences in patient samples, primarily related to medication status. Winsberg et al. (2000) investigated 20 euthymic unmedicated outpatients, type-I or type-II (mean age  $\pm$  S.D. =  $37.9 \pm 13.8$  years); Bertolino et al. (2003) enrolled 17 type I bipolar patients, mostly medicated, on various mood states (mean age  $\pm$  S.D. =  $40.1 \pm 12.9$  years); and Hamakawa et al. (1999) recruited 23 type-I or type-II euthymic medicated bipolar inpatients (mean age  $\pm$  S.D. =  $44.8 \pm 11.0$  years). Therefore, all negative reports involved samples of patients that were primarily on medications, which is consistent with reported effects of lithium in NAA levels in bipolar patients (Moore et al., 2000a). Furthermore, these MRS investigations used various MRS acquisition sequences and methods for metabolite quanti-

fication, which may also have partly accounted for discrepancies. All these studies, including ours, investigated middle-age subjects with homogeneous and clearly defined DSM-IV diagnosis of bipolar disorder (without substance abuse and other psychiatric comorbidities), and utilized reliable procedures for data acquisition and processing.

Negative findings for NAA abnormalities in bipolar disorder were also reported for other brain regions, such as basal ganglia (Bertolino et al., 2003; Hamakawa et al., 1998; Kato et al., 1996; Ohara et al., 1998; Sharma et al., 1992), thalamus (Bertolino et al., 2003), occipital lobes (Bertolino et al., 2003; Sharma et al., 1992), parietal lobes (Stoll et al., 2002), and cingulate (Bertolino et al., 2003). Nonetheless, abnormal levels of NAA in bipolar subjects have recently been reported in hippocampus (low) (Bertolino et al., 2003) and thalamus (high) (Deicken et al., 2001). Therefore, suggestions of neuronal impairment/dysfunction, as reflected by lower NAA levels, have also been reported for other brain regions in bipolar patients.

Interestingly, we found significantly higher NAA/PCr+Cr ratios in lithium-treated bipolar patients compared to unmedicated ones and healthy controls. Consistently, it has been shown that chronic treatment with lithium enhances NAA/PCr+Cr levels in the temporal lobes (Silverstone et al., 2003) and basal ganglia of bipolar patients (Sharma et al., 1992). Also, Moore et al. (Moore et al., 2000a) reported a small but significant increase of total brain NAA levels (5%, combining NAA concentrations from frontal, parietal, occipital, and temporal lobes) after 4 weeks of lithium treatment in 21 individuals, including bipolar patients ( $N=12$ ) and healthy subjects ( $N=9$ ). The results of increased NAA/PCr+Cr levels could be related to the neuroprotective properties of lithium (Manji et al., 2000). Nonetheless, as ratios to PCr+Cr were used, the possibility of confounding effects from changes in PCr+Cr, rather than in NAA, cannot be completely ruled out.

Some potential limitations of the present study should be taken in consideration. First, the relatively small sample size may have reduced the statistical power of our analyses, and small changes in the metabolite concentrations may not have been detected. Second, only the DLPFC was investigated in this study; therefore our findings cannot be extrapolated to other cortical brain areas.

In conclusion, this study did not find abnormally low levels of NAA in DLPFC in adult bipolar disorder, in a sample of patients who were mostly medicated, in contrast to a prior study that found reduced NAA levels in unmedicated bipolar patients. Furthermore, elevated brain NAA/PCr+Cr ratios were found in lithium-treated bipolar patients compared to drug-free bipolar and healthy individuals, which is consistent with the hypothesis that lithium treatment has effects of increasing NAA levels in prefrontal cortex. Longitudinal MRS investigations involving larger samples of untreated patients will be needed to further explore the putative neuroprotective effects of lithium and their relationship to treatment response in bipolar disorder.

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