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Hippocampal ^{1}H MRS in first-episode bipolar I patients

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Abstract

Based on earlier structural and functional neuroimaging studies, we specifically wanted to assess *N*-acetylaspartate (NAA), choline-containing compounds (CHO), and creatine+phosphocreatine (CRE) levels in brain hippocampus previously demonstrated to be involved in the pathophysiology of bipolar disorder which have not been evaluated in first-episode patients. Twelve patients meeting DSM-IV criteria for bipolar disorder who consecutively applied to our department and 12 healthy controls were studied. The patients and controls underwent proton magnetic resonance spectroscopy (^{1}H MRS), and measures of NAA, CHO, and CRE in hippocampal regions were obtained. ANOVA revealed in the hippocampus a significant effect of diagnosis for NAA/CRE and for NAA/CHO but not for CHO/CRE. Post hoc analysis showed that patients had a significant bilateral reduction of NAA/CRE and of NAA/CHO. No significant correlation was found between hippocampus volume and ratio measures. Correlation analyses exhibited significant correlation between NAA values and the YMRS for both side of the hippocampus, but not any other clinical variables (age, age at onset, and duration of illness). In summary, hippocampal neuronal abnormalities seem to be present at the onset of bipolar I disorder. These data suggest that neuronal abnormalities in hippocampus may be associated with the severity of bipolar I disorder. As these data were obtained in patients in their first-episode (all the patients were manic), they cannot be explained by chronicity of illness or pharmacological treatment.

Keywords: Bipolar disorder; Choline; Creatine–phosphocreatine; MRI; *N*-acetylaspartate; Spectroscopy

1. Introduction

A growing number of brain imaging studies have been conducted in patients with bipolar disorder to identify volume changes in specific brain regions, such as the temporal lobes, subcortical structures, and the frontal lobes (Soares and Mann, 1997; Strakowski et al., 2002). Recent brain imaging studies have reported decreased subgenual prefrontal cortex volume (Drevets et al., 1997; Hirayasu et al., 1999), decreased prefrontal gray matter, and amygdala volume increase (Strakowski et al., 1999; Altshuler et al., 2000; Brambilla et al., 2003) in patients with bipolar disorder. Other common findings include an increase in the prevalence of white matter hyperintensities and decreased cerebellar size (Lyoo et al., 2002; Stoll et al., 2000). The published studies of functional neuroimaging in bipolar disorder revealed alterations in glucose metabolism, regional cerebral blood flow or high-energy phosphate metabolism in patients with bipolar disorder in the prefrontal and temporal cortex, basal ganglia and amygdala (Blumberg et al., 1999; Drevets et al., 1997). Functional neuroimaging studies lend further evidence to physiological abnormalities in cortical and subcortical fronto-limbic regions in bipolar disorder. Neuroimaging studies that examine neurochemistry in the living brain provide further support for the hypothesis that bipolar disorder is related to changes in neuronal viability and function. Proton magnetic resonance spectroscopy ($_{1}$H MRS), a recent development in MR technology, allows biochemical constituents to be directly assayed in vivo. *N*-acetylaspartate (NAA), one of the prominent peaks of ^{1}H MRS, has been reported to exist mainly intraneuronally. A reduction of NAA is considered

Abbreviations: CHO, Choline; CRE, Creatine–phosphocreatine; DLPFC, dorsolateral prefrontal cortex; ^{1}H MRS, proton magnetic resonance spectroscopy; HDRS, Hamilton Depression Rating Scale; NAA, *N*-acetylaspartate; YMRS, Young Mania Rating Scale.

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to reflect a loss of neurons and axons and/or neural dysfunction (DeStefano et al., 1995). Choline (CHO), a marker of the membrane phospholipids is increased in myelin breakdown. Creatine–phosphocreatine (CRE) is an energetic marker of cells. Studies using high resolution MRS reveal that unmedicated patients with bipolar disorder have decreased levels bilaterally of NAA in the hippocampus, as compared with healthy control subjects. Moreover, therapeutic doses of lithium reverse these decreased levels of NAA in their brain (Moore et al., 2000). Hippocampal abnormalities in mood disorders have been detected using other methods. For instance, post-mortem studies found abnormalities of interneurons (Benes and Berretta, 2001) and a reduction in the expression of glutamic acid decarboxylase (Heckers et al., 2002) in patients with bipolar disorder, and changes of synaptic protein and cell adhesion molecules in depressive (Jorgensen and Riederer, 1985) and bipolar disorder patients (Vawter et al., 2002). Low NAA is thought to represent loss of neurons and/or axons, reduction of interneuronal neuropil, and neuronal or axonal metabolic dysfunction or damage (Baxter et al., 1989; Drevets, 1999). Deicken et al. (2003) found low NAA bilaterally in the absence of smaller hippocampal volume, supporting the idea that NAA might be a more sensitive marker of neuronal damage or loss than quantitative magnetic resonance imaging measurements of tissue loss. Thus, based on earlier structural and functional neuroimaging studies, we specifically wanted to assess in first-episode bipolar I patients, NAA levels together with CHO and CRE in brain hippocampus previously demonstrated to be involved in the pathophysiology of bipolar disorder.

2. Methods

2.1. Subjects and clinical evaluation

Twelve subjects diagnosed with bipolar I disorder (6 males and 6 females; mean age=28.2 years, SD=6.5) in their first-episode, and 12 psychiatrically well matched subjects (6 males and 6 females; mean age=26.8 years, SD=7.6 years) participated in the study. Diagnoses were made blindly by a team of trained diagnosticians based on a structured clinical interview for DSM-IV. All subjects were right-handed. All subjects meeting the criteria were given details of the study and asked to sign a written informed consent form if they wished to participate. The study was approved by the Local Ethic Committee.

The exclusion criteria include the presence of any comorbid psychiatric disorder, current medical problems, or alcohol/substance abuse within the 6 months preceding the study. Healthy control subjects had no DSM-IV Axis I disorder, nor did their first-degree relatives, as determined by the SCID non-patient version, no current medical problems, neurologic or psychiatric histories, and no use of psychoactive medication within 2 weeks of the study.

The subjects were evaluated by using the Young Mania Rating Scale (YMRS) for manic symptoms (Young et al., 1978) and Hamilton Depression Rating Scale (HDRS) for depressive symptoms (Hamilton, 1960). Scores of twenty or more on the YMRS were necessary for the patients with manic episode. All patients had already scores of 20 or higher (28.9±3.8) on the YMRS. The HDRS mean HDRS score was 4.9±2.1.

2.2. MRI procedure

Multiple-slice ^{1}H MRSI was performed on a conventional GE Signa Excite 1.5-T MR imaging system (GE Medical Systems Milwaukee, WI) equipped with self-shielded gradients using the method of Duyn et al. (1993) as modified by our group; the procedure employed in this study was identical to that used in the Bertolino et al. (2003) report. After a 3 plane localizer, a set of T2-weighted, 5-mm-thick, oblique coronal images (FRFSE-XL, TR=5000 ms, TE=85 ms) was acquired in a plane perpendicular to the sylvian fissure. In each slice, phase encoding procedures were used to obtain a 32×32 array of spectra from voxels. Each voxel had nominal dimensions of 7.5×7.5×15 mm (0.84 mL). Actual volume, based on full width at half maximum (FWHM) after filtering of k-space, was 1.4 mL. The ^{1}H MRSI sequence involves a Probe-P slice selection with TR of 1000 ms and TE of 144 ms for the acquisition. The pulse sequence also includes suppression of water and most of the signal arising from lipids in skull marrow and in surface tissues. From the skull and scalp, to block the lipid signals, the ^{1}H MRSI sequence involved an outer-volume saturation pulse.

A three-dimensional MRI data set was acquired as 124 conventional sagittal slices (spoiled gradient echo pulse sequence [SPGR], TR 24=ms, TE=5 ms), after the second set of T1-weighted images. ^{1}H MRSI data were processed on Workstation (GE functool 2.6.6). NAA, CHO, and CRE peaks were automatically determined for all voxels. Cosine filters were used for apodization of the free induction decay to minimize bleed before Fourier transformation. Voxels in which these metabolite signals cannot be identified (e.g., voxels located outside the head and on or near the skull's surface) were then manually nulled. The signal strength in a range of 0.2 parts per million (ppm; .1 ppm on each side of the center of the peak) around the NAA, CHO, and CRE signal positions was integrated to produce four 32×32 arrays of metabolite signals. A rater blind to diagnosis manually drew the hippocampal region on the T1-weighted coaxial MR images. Afterwards, this was transferred to the same location on the metabolite maps. The hippocampal region was drawn with reference to standard anatomic atlases (Duvernoy and Cabanis, 1991; Bertolino et al., 1996; Talairach and Tournoux, 1998). Voxels that were contained within the anatomic hippocampus but not observed in the metabolite maps were excluded to obtain exact calculations only on containing ^{1}H spectra. Position of hippocampal voxels and sample magnetic resonance spectrum are presented in Fig. 1.

2.3. Statistical analysis

Statistical analyses were conducted using SPSS for Windows software, version 10.0 (SPSS, Chicago, IL). Differences between patients and controls were tested separately for each metabolite ratio by a *one-way analysis of variance (ANOVA)*, with hemisphere

(left or right) as the within-group factor and diagnosis as the between-group factor. Post hoc analysis was performed by Tukey's honestly significance difference test. The non-parametric Mann–Whitney *U* test was used to perform comparisons between patients' sub-groups, as the sample sizes involved were relatively small. Correlations were assessed with Spearman's Test.

3. Results

Bipolar patients and healthy control subjects did not differ in regard to age ($p>0.05$), gender ($p>0.05$), or ICV (1412.4±135.3 and 1446.1±144.5 cm^3, respectively; $p>0.05$), although healthy control subjects presented a non-significant trend toward higher degrees of education than bipolar patients ($p=0.08$). All inter-rater reliability scores were equal to or above 0.80, demonstrating sufficient inter-reliability.

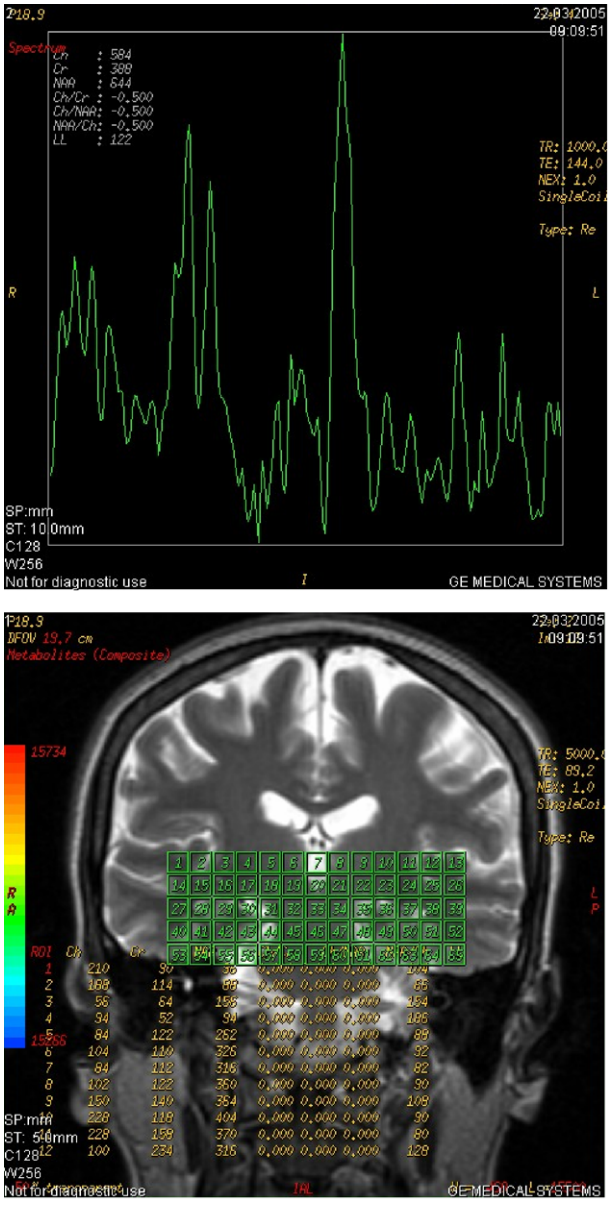

Fig. 1. Position of hippocampal voxels and sample magnetic resonance spectrum.

Table 1
Volumetric measures and hippocampal metabolites of the bipolar patients and healthy controls

	Bipolar patients ($n=12$)	Healthy controls ($n=12$)	p
ICV	1412.4±135.3	1446.1±144.5	>0.05
Whole brain volume	1125.4±127.5	1134.7±140.6	>0.05
Gray matter volume	779.2±80.3	802.3±84.1	>0.05
White matter volume	347.2±23.2	332.4±30.8	>0.05
Left hippocampus	3.82±0.49	3.89±0.55	>0.05
Right hippocampus	3.75±0.43	3.79±0.51	>0.05
NAA/CRE	1.37±0.31	1.72±0.36	<0.01
NAA/CHO	1.10±0.23	1.32±0.22	<0.05
CHO/CRE	1.56±0.19	1.65±0.24	>0.05

ICV = Intracranial volume; NAA = *N*-acetylaspartate; CRE = Creatinine; CHO = Choline.

Table 1 presents the unadjusted mean volumes of measured structures for bipolar patients and healthy controls. Whole brain volume, gray and white matter volumes did not differ between the patient and control groups ($p>0.05$). On the other hand, whole brain volume, gray and white matter volumes still remained statistically non-significant in patients with bipolar disorder after covarying for age.

ANCOVA revealed in the hippocampus a significant effect of diagnosis for NAA/CRE [mean±SD for controls=1.72±0.36, for patients=1.37±0.31; $F=7.9$, $p<0.01$] and for NAA/CHO [mean±SD for controls=1.32±0.22, for patients=1.10±0.23; $F=4.02$, $p<0.05$] but not for CHO/CRE [$F=0.35$ $p>0.05$]. Post hoc analysis showed that patients had a significant bilateral reduction of NAA/CRE ($p<0.01$) and of NAA/CHO ($p<0.05$). No main effect of hemisphere or interaction of diagnosis by hemisphere was found for any metabolite ratio. Further analyses with ANOVA on metabolite ratios in hippocampus to check for gender effects did not reveal any significant effects ($p>0.05$), suggesting that reductions of NAA ratios are not related to gender.

No significant correlation was found between hippocampus volume and ratio measures ($r=-0.19$ and 0.26, for left and right hippocampus in patient group, respectively; and $r=0.29$ and -0.12 in healthy controls, respectively; $p>0.05$). Correlation analyses exhibited significant correlation between NAA values and the YMRS for both side of the hippocampus ($r=0.52$, $p<0.05$ for left and $r=0.52$, $p<0.05$ for right sides), but not any other clinical variables (age, age at onset, and duration of illness).

4. Discussion

To our knowledge, this is the first report of significantly lower NAA in both the right and left hippocampus in first-episode bipolar I disorder patients without psychotic features, relative to healthy comparison subjects. Previous ^1H MRS studies of various brain regions in bipolar disorder reported lower NAA bilaterally in the dorsolateral prefrontal region (Winsberg et al., 2000), as well as normal NAA measures in the lenticular nuclei (Ohara et al., 1998) and frontal lobes (Hamakawa et al., 1999). Since NAA is found only in neurons and axons but not mature glial cells, lower

hippocampal NAA measures suggest loss of neurons and/or axons, reduction of interneuronal neuropil, neuronal or axonal metabolic dysfunction, or some combination of these processes. Nowadays, it has been well-established that psychopharmacological interventions and psychotherapeutic approaches can affect both activity and volumetric measurements of brain regions. Thus, it seems very important to investigate the neurochemical dimension in first-episode bipolar patients. Therefore, we planned this MRS study in patients with bipolar disorder who experienced their first-episode focusing on in vivo neuroanatomy of hippocampus to further evaluate the hypothesis of neurochemical abnormalities in this region in bipolar patients and their possible involvement in the pathophysiology of bipolar disorder.

The present ^{1}H MRS study demonstrated bilateral lower ratios of hippocampus NAA/CRE and NAA/CHO in first-episode bipolar I disorder patients as compared with healthy controls. In addition, we found that there was significant correlation between NAA values and the YMRS for both sides of the hippocampus. NAA is thought to be a measure of neuronal integrity, our findings of decreased NAA/CRE suggest decreased hippocampus neuronal density or neuronal dysfunction in patients with bipolar I disorder. Since in this preliminary study no other brain region has been investigated, it is possible that these findings are not exclusive to the hippocampal region and that other brain regions could show such changes as well.

Previous ^{1}H MRS studies involving various anatomical sites in patients with bipolar disorder have demonstrated conflicting results. Sharma et al. (1992) found increased NAA/CRE in the basal ganglia of bipolar patients. Stoll et al. (1992) and Yurgelun-Todd et al. (1993) found no differences in NAA in the temporal lobes between bipolar and control subjects. Lower NAA measures in mood disorders have been reported. In one of them (Renshaw et al., 1995) in a mixed group of patients with schizophreniform or bipolar disorder, the authors found a reduction of NAA measures in the temporal lobes. Another ^{1}H MRS study showed significant reductions of NAA peaks in the dorsolateral prefrontal cortex (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). Chang et al. (2003) reported reduced NAA levels in DLPFC in a sample of pediatric bipolar patients who had a parent with bipolar disorder. In a more recent study (Bertolino et al., 2003), lower NAA/CRE and NAA/CHO in hippocampus of patients with bipolar disorder were found, as seen in our study. A reduction of NAA and CRE hippocampal concentrations has been shown in another study as well (Deicken et al., 2003). The conflicts and inconsistency in results among a variety of studies aforementioned could be explained by several factors, such as: (1) differences in patient characteristics (sex, handedness, age, illness duration, age at onset, and severity of illness), moreover our patients were with their first-episode; (2) methodological differences in MRS procedure; and (3) limited statistical power of studies demonstrating negative findings. These results are consistent with the present data, and suggest that NAA/CRE reductions in our patients are because of lower levels of NAA. Our data in first-episode manic patients also suggest that neuronal pathology, as reflected by reduction of NAA measures, does not seem an epiphenomenon of chronicity of the disorder or presence of pharmacological treatment but may be associated with the severity of the disorder as suggested by the significant correlation found between NAA values and the YMRS for both sides of the hippocampus.

The strengths of the present study include a well-characterized clinical sample and the use of well-established morphometric MRI methods. The hypothesis-driven nature of this investigation also represents a strength. Nonetheless, some particular limitations in our present findings should be considered. The number of subjects studied was small and the statistical thresholds applied were modest, thereby accentuating these risks and underscoring the importance of replication.

5. Conclusion

In summary, hippocampal neuronal abnormalities seem to be present at the onset of bipolar I disorder. These data suggest that neuronal abnormalities in hippocampus may be associated with the severity of bipolar I disorder. As these data were obtained in patients at first-episode (all the patients were manic), they cannot be explained by chronicity of illness or pharmacological treatment. Future longitudinal neuroimaging and neuropsychological studies with larger patient samples are warranted in order to confirm these preliminary findings to better characterize the relevance of neurochemical abnormalities in hippocampus in the pathophysiology of bipolar disorder.

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