Psychiatry and Clinical Neurosciences 2009; **63**: 486–490 doi:10.1111/j.1440-1819.2009.01993.x

Regular Article

Neurochemistry of the hippocampus in patients with obsessive–compulsive disorder

Murad Atmaca, MD,[1]* Hanefi Yildirim, MD,[2] Huseyin Ozdemir, MD,[2] Mustafa Koc, MD,[2] Sinan Ozler, MD[1] and Ertan Tezcan, MD[2]

[1]*Department of Psychiatry, School of Medicine, Firat University, Elazig and* [2]*Department of Psychiatry, School of Medicine, Maltepe University, Istanbul, Turkey*

Aim: To date, despite possible neuroanatomical importance, no magnetic resonance spectroscopy (MRS) study on hippocampus has been performed in obsessive–compulsive disorder (OCD). The purpose of the present study was therefore to compare hippocampal chemicals in patients with OCD with those in healthy subjects with no psychopathology.

Methods: Eighteen patients meeting DSM-IV criteria for OCD and 18 healthy controls were studied. The patients and controls underwent proton magnetic resonance spectroscopy (^{1}H-MRS), and measures of *N*-acetyl-l-aspartate (NAA), choline (CHO), and creatine (CRE) in hippocampal regions were obtained.

Results: Both NAA/CRE and NAA/CHO ratios in the hippocampus in patients with OCD were reduced relative to healthy controls. The ANOVA showed a near-significant effect of diagnosis for NAA/CRE and a significant effect for NAA/CHO, but the ANOVA did not show any significant effect even at a trend level for CHO/CRE. No main effect of hemisphere was found for any metabolite ratio.

Conclusions: The presence of neuronal degeneration is suggested in OCD. 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 OCD.

Key words: choline, magnetic resonance spectroscopy, *N*-acetylaspartate, obsessive–compulsive disorder, spectroscopy.

GROWING NEUROIMAGING STUDIES have the potential to increase our understanding of the connection between the clinical features and related neurobiology in obsessive–compulsive disorder (OCD). Magnetic resonance spectroscopy (MRS), an increasing trend in psychoneuroradiology, is a safe and non-invasive technique for the *in vivo* study of brain chemistry and metabolism. MRS has been used primarily to measure concentrations of metabolites in brain tissue such as *N*-acetyl-aspartate (NAA; a marker of neuronal viability), combined glutamate and glutamine, choline (CHO; a marker of cell membrane turnover), myo-inositol, and creatine–phosphocreatine (CRE; a marker of cellular energy). NAA has been reported to exist mainly intraneuronally. A reduction of NAA is considered to reflect a loss of neurons and axons and/or neural dysfunction.[1] CHO, a marker of the membrane phospholipids, is increased in myelin breakdown. CRE is an energetic marker of cells. The majority of current functional and structural neuroimaging findings have emphasized abnormalities in fronto-striatal–thalamic–cortical circuits, but other candidate structures include the hippocampus–amygdala complex. Hippocampal and amygdalar abnormalities were emphasized in studies involving positron emission tomography or functional magnetic resonance imaging and authors commented that the region

**Correspondence: Murad Atmaca, MD, Firat (Euphrates) Universitesi, Firat Tip Merkezi, Psikiyatri Anabilim Dali, 23119 Elazig, Turkey. Email: matmaca_p@yahoo.com*
Received 22 May 2008; revised 16 March 2009; accepted 1 April 2009.

might play an important role in the pathophysiology of OCD.[2,3] In contrast, it has been suggested that hippocampal structural alteration may play a role in the pathophysiology of OCD.[3] Furthermore, the agents that are efficacious in the management of OCD (e.g. serotonergic re-uptake inhibitors [SSRI], and anti-anxiety drugs) have been shown to exert their effects on receptors in the amygdaloid.[4–6] Although limited studies have been performed and no consensus has been established in MRS studies in OCD, some clues were obtained. Two studies found unilaterally decreased NAA in the striatum of adults with OCD,[7,8] and two reported increased concentrations of CHO bilaterally in the medial thalami of children with OCD.[9,10] In addition, in another study Rosenberg *et al*. found that increased glutamine concentrations in the left caudate decreased after management of pediatric OCD.[11] In another study, absolute levels of NAA were shown to be increased in the right dorsolateral prefrontal cortex.[12] Most recently, Sumitani *et al*. suggested that a subgroup of OCD patients who respond to an SSRI with an atypical antipsychotic had lower NAA levels in the anterior cingulate compared to those on SSRI treatment alone.[13] To date, however, despite possible neuroanatomical importance, no MRS study on the hippocampus has been performed in OCD. The purpose of the present study was therefore to compare hippocampal chemicals in patients with OCD with those in healthy subjects with no psychopathology.

METHODS

Subjects and clinical evaluation

There were two age- and sex-matched groups: OCD and healthy subjects. Each group consisted of 18 subjects (12 women, six men), who were all right handed, and had a mean age of 28.1 ± 3.4 years and 30.6 ± 4.2 years, respectively. DSM-IV diagnoses were obtained using the Turkish version of the Structured Clinical Interview for DSM-IV (SCID).[14] Patients were recruited from Firat University School of Medicine Department of Psychiatry. They were either not on medication or not taking any psychoactive drug during the last 2 weeks. Normal volunteers were recruited from the hospital staff. This study was carried out according to Helsinki Declaration guidelines. Written informed consent was obtained from all subjects.

The exclusion criteria included the presence of any current or history of 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 disorders in self or in a first-degree relative, as determined on 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 severity of OCD was evaluated using the Yale–Brown Obsession Compulsion Scale (Y-BOCS).

Magnetic resonance imaging

MRI and MRS were carried out on a 1.5-Tesla GE Signa Excite high-speed scanner (General Electric, Milwaukee, WI, USA). A high-resolution structural image of the entire brain was obtained using sagittally acquired 3-D spiral fast spin echo high-resolution images (repetition time [TR], 2000 ms; echo time [TE], 15.6 ms; field of view [FOV], 240 mm; flip angle, 20°; bandwidth, 20.8 kHz; slice thickness, 2.4 mm; echo spacing, 15.6 ms, 8 echoes; matrix size, 240 × 192; resolution, 0.9375 × 0.9375 × 2.4 mm). Anatomic measurements were obtained on a computer advanced workstation with the GE Volume Viewer voxtool 4.2 (GE Medical Systems, Milwaukee, WI, USA). Each voxel had nominal dimensions of 10 mm × 10 mm × 2.4 mm (0.24 mL) with an actual volume of 0.4 mL, based on full width at half maximum. The hippocampal region was drawn with reference to standard anatomic atlases.[15–17]

We investigated following the neurochemical markers: NAA, CRE, and CHO. For all voxels, NAA, CHO, and CRE peaks were determined automatically. The signal strength around the NAA, CHO, and CRE signal positions was integrated to produce three 18 × 18 arrays of metabolite signals. Position of hippocampal voxels and sample magnetic resonance spectrum are presented in Fig. 1.

Statistical analysis

Statistical analysis was conducted using SPSS for Windows software, version 10.0 (SPSS, Chicago, IL, USA). For each metabolite ratio, differences between patients and controls were tested separately on 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 analyses

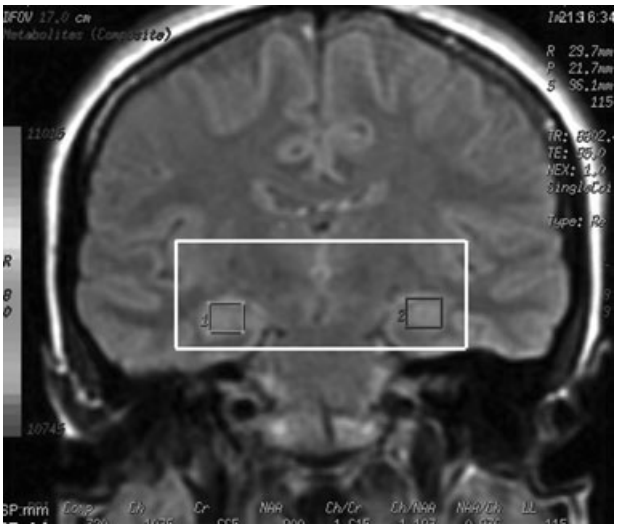

Figure 1. Position of hippocampal voxels and sample magnetic resonance spectrum.

were performed using Tukey's honestly significance difference test. Group differences in demographic variables involving continuous data were computed using independent *t*-test. Between-group comparisons involving categorical data were assessed using χ^2 test. Correlations were assessed with Pearson's correlation test.

RESULTS

As can be seen in Table 1, the patients and controls did not differ with regard to age, gender, intracranial volume, whole brain volume, gray or white matter volumes ($P > 0.05$).

The ANOVA showed a near-significant effect of diagnosis for NAA/CRE ($F = 3.8$, $P = 0.06$; mean ratio, 1.13 ± 0.21 for patients and 1.31 ± 0.28 for controls) and a significant effect for NAA/CHO ($F = 6.8$, $P < 0.01$; mean ratio, 2.87 ± 0.29 for patients 3.99 ± 0.37 for controls). But the ANOVA did not indicate any significant effect even at trend level for CHO/CRE ($F = 1.26$, $P > 0.05$). No main effect of hemisphere was found for any metabolite ratio.

The Spearman correlation test did not find any relationship in either group between the NAA/CRE, NAA/CHO or CHO/CRE ratio of the hippocampus and age, years of education, age of onset, duration of illness, or total Y-BOCS score, except for a negative correlation between the NAA/CHO ratio and age ($r = -0.53$, $P < 0.05$).

DISCUSSION

The present results show a decreases in both NAA/CRE and NAA/CHO ratios in the hippocampus in patients with OCD relative to healthy control subjects and also a relationship between NAA/CHO ratio and age in the patient group. Because NAA is thought to be a measure of neuronal integrity, these findings of decreased NAA/CRE and NAA/CHO may suggest decreased hippocampal neuronal density or at least neuronal dysfunction in patients with OCD. We did

Table 1. Subject characteristics

	OCD patients ($n = 18$)	Controls ($n = 18$)
Age (years)	28.1 ± 3.4	30.6 ± 4.2
Gender (F/M)	12/6	12/6
Age at onset (years)	22.6 ± 4.2	–
Graduated from high school	11	13
Handedness (right)	18	18
Presence of family history	2	1
YBOCS score	17.2 ± 3.0	–
ICV (cm^3)	1448.7 ± 180.5	1513.4 ± 206.2
Whole brain volume (cm^3)	1251.1 ± 110.3	1194.9 ± 91.8
Gray matter volume (cm^3)	847.6 ± 86.2	819.1 ± 90.4
White matter volume (cm^3)	403.5 ± 36.1	375.8 ± 28.2
Hippocampus volume (mm^3)		
Left	2339.7 ± 226.5	2681.8 ± 369.2*
Right	2289.9 ± 200.6	2711.3 ± 306.3*
NAA/CRE	1.16 ± 0.21	1.31 ± 0.28*
NAA/CHO	2.94 ± 0.29	3.99 ± 0.37**
CHO/CRE	0.39 ± 0.14	0.41 ± 0.11
NAA (mmol/kg)	8.62 ± 1.16	9.33 ± 0.93*
CHO (mmol/kg)	2.93 ± 0.38	2.33 ± 0.20*
CRE (mmol/kg)	7.45 ± 1.62	7.12 ± 1.48

*$P < 0.05$; **$P < 0.01$.
No significant differences existed between groups in age, handedness, education, and gender composition.
CHO, choline; CRE, creatine–phosphocreatine; ICV, intracranial volume; NAA, *N*-acetyl aspartate; Y-BOCS, Yale–Brown obsession compulsion scale.

not evaluate other brain regions in this preliminary study, however, so we do not know exactly but it is possible that these findings are not specific for the hippocampus and that this finding may be generalized to other brain regions as well. It is unclear whether NAA/CRE decrease is due to an neurodegenerative process or to a trait characteristic of the disorder. The fact that there was a negative correlation between NAA/CHO ratio and age suggests that this may be a neurodegenerative process. In regard to CHO, we found increased concentrations in the patient group compared to healthy controls. There have been studies that did not report CHO changes in adult or pediatric patients with OCD.[8] Recent proton MRS studies have found localized functional neurochemical marker alterations in the left and right medial but not the lateral thalamus.[9,17] In another study, CHO concentrations were reported as significantly increased in the thalamus of 11 treatment-naive pediatric OCD patients. Likewise, Smith *et al*. found that localized functional neurochemical marker alterations in medial thalamic CHO differentiated patients with OCD from healthy control subjects and patients with major depressive disorder.[10] It was suggested that the CHO signal rise might be an important biomarker in specific neuropsychiatric disorders,[9,18] supporting our comment regarding possible neurodegeneration. Meanwhile phosphotidylcholine breakdown has been shown to play an important role in signal transduction,[19] suggesting that altered CHO concentrations in patients with OCD may contribute to the pathophysiology of the disorder in this way. Similarly for NAA concentration, we did not evaluate other brain regions in this preliminary study, so we do not know exactly but it is possible that these findings are not specific for the hippocampus and that they may be generalized to other brain regions as well. To provide strong evidence, however, further investigation with more patients and in multiple brain regions are needed.

Some limitations of the present study should be taken in consideration. First, the relatively small sample size might have reduced the statistical power of the analysis, and small changes in the metabolite concentrations might not have been detected. Second, only the hippocampus was investigated, therefore the present findings cannot be extrapolated to other brain regions.

In conclusion, the present study found that both NAA/CRE and NAA/CHO ratios in the hippocampus in patients with OCD relative to healthy control subjects were reduced, thereby suggesting neuronal degeneration. 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 OCD.

REFERENCES

1 Destefano N, Matthews P, Antel JP, Preul M, Francis G, Arnold DL. Chemical pathology of acute demyelinating lesions and its correlations with disability. *Ann. Neurol.* 1995; **8**: 901–909.
2 McGuire PK, Bench CJ, Frith CD, Marks IM, Frackowiak RS, Dolan RJ. Functional anatomy of obsessive–compulsive phenomena. *Br. J. Psychiatry* 1994; **164**: 459–468.
3 Adler CM, McDonough-Ryan P, Sax KW, Holland SK, Arndt S, Strakowski SM. fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder. *J. Psychiatr. Res.* 2000; **34**: 317–324.
4 Nagy J, Zambo K, Decsi L. Anti-anxiety action of diazepam after intra-amygdaloid application in the rat. *Neuropharmacol* 1979; **18**: 573–576.
5 Gonzalez LE, Andrews N, File SE. 5-HT1A and benzodiazepine receptors in the basolateral amygdala modulate anxiety in the social interaction test, but not in the elevated plus-maze. *Brain Res.* 1996; **732**: 145–153.
6 Zangrossi H Jr, Viana MB, Graeff FG. Anxiolytic effect of intra-amygdala injection of midazolam and 8-hydroxy-2-(di-n-propylamino)tetralin in the elevated T-maze. *Eur. J. Pharmacol.* 1999; **369**: 267–270.
7 Ebert D, Speck O, König A, Berger M, Hennig J, Hohagen F. 1H-magnetic resonance spectroscopy in obsessive-compulsive disorder: Evidence for neuronal loss in the cingulate gyrus and the right striatum. *Psychiatry Res.* 1997; **74**: 173–176.
8 Bartha R, Stein MB, Williamson PC *et al.* A short echo 1H spectroscopy and volumetric MRI study of the corpus striatum in patients with obsessive-compulsive disorder and comparison subjects. *Am. J. Psychiatry* 1998; **155**: 1584–1591.
9 Rosenberg DR, Amponsah A, Sullivan A, MacMillan S, Moore GJ. Increased medial thalamic choline in pediatric obsessive–compulsive disorder as detected by quantitative in vivo spectroscopic imaging. *J. Child Neurol.* 2001; **16**: 636–641.
10 Smith EA, Russell A, Lorch E *et al.* Increased medial thalamic choline found in pediatric patients with obsessive–compulsive disorder versus major depression or healthy control subjects: A magnetic resonance spectroscopy study. *Biol. Psychiatry* 2003; **54**: 1399–1405.
11 Rosenberg DR, MacMaster FP, Keshavan MS, Fitzgerald KD, Stewart CM, Moore GJ. Decrease in caudate

glutamatergic concentrations in pediatric obsessive–compulsive disorder patients taking paroxetine. *J. Am. Acad. Child Adolesc. Psychiatry* 2000; **39**: 1096–1103.
12 Russell A, Cortese B, Lorch E *et al.* Localized functional neurochemical marker abnormalities in dorsolateral prefrontal cortex in pediatric obsessive–compulsive disorder. *J. Child Adolesc. Psychopharmacol.* 2003; **13**: S31–S38.
13 Sumitani S, Harada M, Kubo H, Ohmori T. Proton magnetic resonance spectroscopy reveals an abnormality in the anterior cingulate of a subgroup of obsessive–compulsive disorder patients. *Psychiatry Res.* 2007; **154**: 85–92.
14 Corapcioglu A, Aydemir Ö, Yıldız M *et al. DSM-IV Eksen I Bozuklukları (SCID-I) İçin Yapılandırılmış Klinik Görüşme, Klinik Versiyon*. Hekimler Yayın Birliği, Ankara, 1999.
15 Duvernoy HM, Cabanis EA. *The Human Brain: Surface, Three-Dimensional Sectional Anatomy, and MRI*. Springer-Verlag, New York, 1991.
16 Talairach J, Tournoux P. *Coplanar Stereotaxic Atlas of the Human Brain*. Thieme Medical Publishers, New York, 1998.
17 Fitzgerald KD, Moore GJ, Paulson LA, Stewart CM, Rosenberg DR. Proton spectroscopic imaging of the thalamus in treatment-naive pediatric obsessive–compulsive disorder. *Biol. Psychiatry* 2000; **47**: 174–182.
18 Steingard RJ, Yurgelun-Todd DA, Hennen J *et al.* Increased orbitofrontal cortex levels of choline in depressed adolescents as detected by in vivo proton magnetic resonance spectroscopy. *Biol. Psychiatry* 2000; **48**: 1053–1061.
19 Exton JH. Phosphatidylcholine breakdown and signal transduction. *Biochim. Biophys. Acta* 1994; **1212**: 26–42.