The Hippocampus in Patients Treated With Electroconvulsive Therapy

A Proton Magnetic Resonance Spectroscopic Imaging Study

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Background: We monitored the effect of electroconvulsive therapy (ECT) on the nuclear magnetic resonance–detectable metabolites N-acetylaspartate, creatine and phosphocreatine, and choline-containing compounds in the hippocampus by means of hydrogen 1 magnetic resonance spectroscopic imaging. We hypothesized that if ECT-induced memory deterioration was associated with neuronal loss in the hippocampus, the N-acetylaspartate signal would decrease after ECT and any increased membrane turnover would result in an increase in the signal from choline-containing compounds.

Methods: Seventeen patients received complete courses of ECT, during which repeated proton magnetic resonance spectroscopic imaging studies of the hippocampal region were performed. Individual changes during the course of ECT were compared with values obtained in 24 healthy control subjects and 6 patients remitted from major depression without ECT.

Results: No changes in the hippocampal N-acetylaspartate signals were detected after ECT. A significant mean increase of 16% of the signal from choline-containing compounds after 5 or more ECT treatments was observed. Despite the mostly unilateral ECT application (14 of 17 patients), the increase in the choline-containing compound signal was observed bilaterally. Lactate or elevated lipid signals were not detected. All patients showed clinical amelioration of depression after ECT.

Conclusions: Electroconvulsive therapy is not likely to induce hippocampal atrophy or cell death, which would be reflected by a decrease in the N-acetylaspartate signal. Compared with an age-matched control group, the choline-containing compounds signal in patients with a major depressive episode was significantly lower than normal, before ECT and normalized during ECT.

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Electroconvulsive therapy (ECT) is highly effective in the treatment of major depression and other selective psychiatric disorders. Nevertheless, ECT remains controversial because of its cognitive side effects and its unknown effects on cerebral function. Structural brain imaging and postmortem neuropathologic studies, however, provided no evidence that ECT produces brain damage. Human brain imaging studies are limited in their spatial resolution and cannot detect neuronal damage at the cellular level. Measurements of water T2 relaxation times showed a significant increase in T2 in the thalamus after ECT. It has been observed that after ECT, acetylcholine levels in cerebrospinal fluid rise, accompanied by increased activity of cholinesterase in cerebrospinal fluid and blood. Results of recent animal studies have shown that mossy fiber sprouting in limbic brain regions is induced by multiple ECT treatments. To our knowledge, no magnetic resonance spectroscopic imaging (MRSI) studies have been reported monitoring the effects of ECT on the hippocampus. Three single-voxel hydrogen 1 (1H) and phosphorus 31 studies have reported pre- and post-ECT spectra in other brain regions, and the 1H MRSI studies were aimed at lactate detection after ECT.

Known adverse effects of ECT are transient anterograde amnesia, involving rapid forgetting of newly learned information, and retrograde amnesia, involving loss of memory for information learned before treatment, which might be persistent or permanent. This association of ECT with a classic amnestic syndrome involving anterograde and retrograde amnesia implicates a dysfunction in medial temporal lobe structures, especially the hippocampus. Therefore, metabolite changes after ECT could be expected in this region. We hypothesized that 2 types of metabolic changes might be induced by ECT. First is a decrease of N-acetylaspartate (NAA) due
to neuronal loss, which would be reflected in a permanent NAA decrease, or dysfunction, which could be associated with a reversible NAA decrease in the hippocampus. Both types of NAA decrease could explain a memory deterioration. Second is an increase in the signal from choline-containing compounds (Ch) due to an increased membrane turnover possibly related to hippocampal mossy fiber sprouting. The creatine (Cr) level in the brain is supposed to be relatively stable17 and therefore was not expected to be affected by ECT. As a consequence of the time between the actual ECT and our MRSI measurement of at least 30 hours we did not expect to find an elevated lactate level. Furthermore, lactate could not be detected in the previous single-voxel studies11-13 aimed at detecting a lactate increase. Woods and Chiu12 reported elevated lipid signal levels after ECT using an echo time of 30 milliseconds. We chose an echo time of 135 milliseconds for our MRSI studies, which is not suitable for lipid detection but produces less baseline distortions and thus facilitates evaluation of NAA, Cr, and Ch signals.

The purpose of this study was to monitor quantitative changes of the NAA and Ch signals in the hippocampal region of patients during the course of repetitive ECT sessions.

HIPPOCAMPAL METABOLITE VALUES IN HEALTHY CONTROLS

The metabolite signals of NAA, Cr, and Ch in the healthy control group (n=24) were tested for age-related effects using a Spearman ρ correlation coefficient. This yielded no significant correlations for NAA (Spearman ρ = 0.20, P = .35, 2-tailed) and Cr (Spearman ρ = 0.25, P = .25, 2-tailed). The Ch signal was significantly correlated with age: Ch increased with increasing age (Spearman ρ = 0.51, P = .01, 2-tailed). A linear regression analysis based on the control data was used for age correction of all 3 metabolite signals in the further analysis. No sex-related differ-
acquired. The transverse images were angulated parallel to the long axis of the hippocampus. Point resolved spectroscopy (PRESS) volume prescan was performed parallel to the transverse images and included both hippocampi.23 Patients were carefully positioned to avoid a sideward tilt of the head, enabling the MRI and MRSI volumes to be centered on the midline of both hippocampi. This procedure ensures that voxels obtained from successive MRSI measures of the same individual could be selected from identical locations. Figure 1 illustrates the oblique transverse orientation of the MRI slice and MRSI volume and their reproducibility in 2 data sets obtained in a patient undergoing ECT. An MRSI field of view of 210 × 210 mm and a PRESS volume thickness of 15 mm was used with circular k-space sampling equivalent to a maximum of 24 × 24 phase encoding steps.24 Other measurement parameters included repetition time of 1.8 seconds and echo time of 135 milliseconds, resulting in a measurement time of 13 minutes. Total measurement time was approximately 40 minutes, including setup time and acquisition of 1 MRSI data set.

**MRSI DATA PROCESSING**

An average of 6 voxels (range, 2-8 voxels) from each hippocampus, including primarily tissue from the hippocampal body, were selected for evaluation. Anterior voxels were avoided because of the poorer spectral quality in this region and the suboptimal excitation profile of the 180° selective pulse in the anteroposterior direction of the volume of interest. This, in combination with the chemical shift displacement error of 2.4 mm between NAA and Ch in the in-plane directions (0.8 mT/m gradient strength), leads to disturbed ratios in the first 2 voxels from the anterior and posterior borders of the volume of interest. Care was taken to choose voxels from repetitive measurements of one patient from identical locations because metabolite signal intensities can vary with location within the region of one hippocampus.25 Per data set, mean values of spectra from the left and right hippocampus are reported and added spectra are shown in Figure 1, A and B.

**CLINICAL RESPONSE TO ECT AND METABOLITE CHANGES INDUCED BY ECT**

All patients showed clinical amelioration of depression after ECT (≥50% reduction in HAM-D score). The final HAM-D values ranged from 3.0 to 12.0 (mean 7.4 ± 2.9). A summary of the patient information, number of ECT treatments, and HAM-D scores before and after ECT is given in the Table.

<table>
<thead>
<tr>
<th>Patient</th>
<th>ECT Treatments</th>
<th>HAM-D Before ECT</th>
<th>HAM-D After ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
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<td>2.4</td>
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</tr>
<tr>
<td>Patient 5</td>
<td>2</td>
<td>8.2</td>
<td>3.7</td>
</tr>
</tbody>
</table>

For between-group analysis of intraindividual metabolite signal changes, the differences ΔNAA, ΔCr, and ΔCh between measurements 1 and 2 were used. For patients undergoing ECT this was metabolite signals after minus before ECT; for healthy controls this was the difference between 2 data sets acquired at least 4 weeks apart.
A general linear model with Tukey correction for multiple comparisons, with ΔNAA, ΔCr, and ΔCh as dependent variables and treatment group (ECT group, n=17; healthy control group, n=5) as the between-subject factor was applied. This comparison yielded no significant differences for ΔNAA (F₁,20 =1.17, P =.29) and ΔCr (F₁,20 =0.34, P =.56) but a highly significant difference for ΔCh (ΔChECT=1.20±0.82 and ΔChcontrols =−0.08±0.90; F₁,20 =9.02, P =.007). The Tukey correction for multiple comparisons revealed a substantially different Ch signal between patients before ECT and controls and between patients before ECT and remitted patients treated with amitriptyline (P<.001 for both).

The metabolite signals after ECT were evaluated with the same general linear model. No significant group differences were found (NAA: F₂,44 =1.39, P =.26; Cr: F₂,44 =0.64, P =.53; and Ch: F₂,44 =0.78, P =.46). In a Tukey post hoc test with correction for multiple comparisons, P >.25 for NAA, Cr, and Ch in comparisons among post-ECT patients, amitriptyline-treated patients, and healthy controls. Figure 3 illustrates these findings with box-plots of the age-corrected signals of NAA, Cr, and Ch in patients before and after ECT, remitted patients treated with amitriptyline, and healthy controls.

**COMMENT**

This investigation yielded 2 clear conclusions. First, NAA is stable in the hippocampus throughout a course of ECT. Second, Ch seems to be lower in the hippocampus of patients with a major depressive episode compared with controls and increases during a successful course of ECT. The MRSI-detectable Ch signal has been found to be altered in the basal ganglia in depressed patients, but the direction of the changes is controversial. In addition, results of our study confirm the age-related increase previously reported for choline in vivo proton MR spectra. The fact that NAA remains stable...
The MRSI-detectable Ch signal represents the quaternary N-methyl groups of a variety of Ch. The MRSI resonance is composed of acetylcholine, phosphocholine, glycerophosphocholine, and free choline. Most of the signal arises from phosphocholine and glycerophosphocholine, free choline is less than 5%, and the contribution from acetylcholine is negligible. An increased Ch signal most likely reflects an increase in membrane turnover.

Throughout a course of ECT is consistent with a host of neuropathologic and volumetric evidence after ECT. The finding in this study of stable NAA signals implies that there is no hippocampal atrophy, neuronal damage, or cell death induced by ECT. The question of whether a hippocampal dysfunction would be reflected in measurable NAA loss has not yet been answered.

As expected, we did not find elevated lactate levels, which is probably due to the 30-hour interval between the actual ECT and MRSI measurement. Moreover, lactate could not be detected in the previous single-voxel studies, which were carried out to detect a lactate in-crease.

The Ch signal increase seen during a course of ECT might well reflect a metabolic reaction induced by ECT. The MRSI-detectable Ch signal represents the quaternary N-methyl groups of a variety of Ch. The Ch resonance is composed of acetylcholine, phosphocholine, glycerophosphocholine, and free choline. Most of the signal arises from phosphocholine and glycerophosphocholine, free choline is less than 5%, and the contribution from acetylcholine is negligible. An increased Ch signal most likely reflects an increase in membrane turnover.

Phosphatidylcholine, the major choline-containing metabolite of the normal brain, is MR invisible in myelin, cell membranes, and other brain lipids under normal circumstances. However, under certain conditions, visible choline might be released from this pool. From the acquired 1H spectra it cannot be determined what happened to specific choline compounds. The most likely explanation is increased membrane phospholipid turnover. An alternative explanation of the results might be an increase of the Ch T2 relaxation. This is unlikely because it would necessitate an increase in the Ch T1 relaxation time by a factor of 2.2 to account for a 25% signal increase, assuming a normal T2 of about 330 milliseconds. Such a marked change in relaxation time in an essentially stable cellular environment is unlikely.

Proton decoupled phosphorous 31 spectroscopy offers the possibility to distinguish between glycerophosphocholine and phosphocholine. But phosphorous 31 MRSI is much less sensitive than 1H MRSI, and, hence, spatial resolution is poor and measurement time is prolonged.

Several authors recently reported studies on the effect of ECT on the expression of growth factors in brain, as well as alterations in the function and structure of certain populations of neurons. Duman and Vaidya hypothesize that ECT and antidepressant drug use, via regulation of neurotrophic factors, reverse the atrophy of stress-vulnerable neurons or protect these neurons from further damage. These assumptions are based on results of recent studies suggesting that the pathophysiological mechanism of stress and depression involves atrophy or death of hippocampal neurons. The finding of hippocampal atrophy in depression is not without controversy. In one study, hippocampal volume was not found to discriminate a typical clinical population of older depressed patients from age-similar control subjects. Nevertheless, relations between hippocampal volumes and clinical phenomena in depressed patients, but not in controls, were found. These findings have been interpreted as potentially meaningful interactions between hippocampal structure and the expression of major depression in older persons.

Vaidya et al and Gombos et al reported that long-term administration of ECT induces sprouting of the granule cell mossy fiber pathway in the hippocampus in ani-
mals. This sprouting depends on repeated administration of ECT, reaches a maximum 12 days after the last treatment, and is long lasting (ie, up to 6 months). Multiple seizures- and ECT-induced sprouting occurs in the absence of neuronal loss, indicating that sprouting is not a compensatory response to cell death. This is different from the sprouting induced by kindling or excitotoxin treatment, which induce cell death along with recurrent seizures. Vaidya et al9 conclude that although the functional consequences remain unclear, sprouting of the mossy fiber pathway would seem to oppose the actions of stress and could thereby contribute to the therapeutic actions of ECT. Stringer et al10 previously examined the relation between cell death and sprouting of the mossy fibers. Repeated seizures of the hippocampal-parahippocampal circuit were elicited in anesthetized rats. The authors found that the same number of repeated seizures that caused sprouting of the mossy fibers did not cause detectable cell death or severe stress in any cells within the hippocampus, subicular region, or adjacent entorhinal cortex. From these experiments, the authors conclude that repeated seizures of the hippocampal-parahippocampal circuits can cause sprouting of mossy fibers in the absence of evidence of cell death. Our MRSI findings of increased Ch signal in the absence of decreased NAA signal are concordant with an increased membrane turnover without neuronal loss or damage. These results might be explicable by the observations of mossy fiber sprouting in the hippocampus. Our findings may open a new direction aimed at understanding the metabolic mechanisms underlying ECT response and suggest that a loss of trophic activation in the hippocampus could be the underlying factor in depressive illness.

This study has several limitations. Memory and other cognitive functions were not quantitatively assessed before and after ECT and thus could not be correlated to the observed Ch signal increase after ECT. Our MRSI study was spatially limited to the hippocampal region. Therefore, it is not known whether the observed changes in the Ch signal are solely restricted to the hippocampus. Another brain region where physiological effects of ECT on blood flow, glucose metabolism, and electroencephalographic slow-wave activity were found is the prefrontal cortex. Because patient compliance is crucial for our MRSI studies, it was not possible to put the patients through a prolonged MRSI examination including the prefrontal cortex. On the other hand, the size of the MRSI voxels is relatively large and only averaged data from all hippocampal subregions, such as CA1 and CA3, with known sensitivity to alterations due to seizure, could be obtained. If changes in NAA were to occur strictly localized to a small subfield, our method might not be sensitive enough to detect them. Furthermore, the noninvasive method of MRSI yields only one MRSI signal consisting of a variety of choline-containing compounds and thus the true nature of the Ch signal increase remains unresolved. At present, the interpretation of our results that the Ch signal increase reflects mossy fiber sprouting remains a hypothesis and requires a better understanding of the origin of the increased Ch signals.

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REFERENCES


Figure 3. Boxplots of the age-corrected signals of N-acetylaspartate (NAA) (A), creatine (Cr) (B), and choline-containing compounds (Ch) (C) in patients before and after electroconvulsive therapy (ECT) (n=17), remitted patients treated with amitriptyline (n=6), and healthy control subjects (n=24). AU indicates arbitrary units; circles, patient values outside 95% confidence limits.