The Hippocampus in Patients Treated With Electroconvulsive Therapy

A Proton Magnetic Resonance Spectroscopic Imaging Study

Gabriele Ende, PhD; Dieter F. Braus, MD; Sigrid Walter, MSc; Wolfgang Weber-Fahr, MSc; Fritz A. Henn, MD, PhD

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.

Arch Gen Psychiatry. 2000;57:937-943

From Nuclear Magnetic Resonance Research in Psychiatry, Central Institute of Mental Health, Mannheim, Germany.

©2000 American Medical Association. All rights reserved.
PATIENTS AND METHODS

PATIENTS

Twenty-three inpatients of the Central Institute of Mental Health in Mannheim, Germany, with major depressive episodes were studied with proton MRSI of the hippocampal region. Seventeen patients underwent ECT and 6 were remitted from major depression under treatment with amitriptyline hydrochloride. The latter 6 patients had not previously undergone ECT. The patients were consecutively recruited, the purpose and the procedures of the study were explained to all participants, and written informed consent was obtained. All depressed patients met DSM-IV26 and International Classification of Diseases, 10th Revision,19 criteria for major depressive episodes on the basis of a structured clinical diagnosis interview (including Hamilton Depression Rating Scale [HAM-D]; 21 items, score ≥19). A summary of the subjects’ clinical history is provided in the Table. Of 17 patients undergoing ECT, 12 were psychotic. All patients undergoing ECT were right-handed. The HAM-D score in patients undergoing ECT ranged from 19 to 35 (mean ± SD, 27.7 ± 4.9) before ECT started. Patients underwent 5 to 18 treatments of ECT, and 1 patient underwent 2 ECT courses 6.5 months apart.

The 6 remitted patients and 24 healthy subjects were studied as control groups. Three individuals were studied 4 times and 2 were studied twice with the same protocol for comparison of the longitudinal variability of the metabolite signals. Healthy controls were recruited from the hospital staff and family members and friends of the investigators.

Patients and controls with a history of neurologic or psychiatric disorders other than depression were excluded from our study. A further exclusion criterion was substance abuse, with the exception that 2 patients undergoing ECT with mild alcohol abuse were included. Those 2 patients were abstinent at the time of ECT.

ECT TREATMENTS

Electroconvulsive therapy was administered 3 times per week with a square-wave, brief-pulse, constant-current device (Thymatron DG; Somatics Inc, Lake Bluff, Ill). The standard bifrontotemporal placement and the d’Elia20 placement of electrodes were used for bilateral and unilateral treatment, respectively. Stimulus intensity was determined as a function of age21 and was successively readjusted individually with the goal to stimulate at least 20 to 25 seconds of tonic-clonic movement or 25 to 30 seconds of electroencephalographic seizure activity.22

Fourteen patients were administered exclusively unilateral right-sided ECT at a stimulus intensity of 40% to 100% (100% = 504 millicolombs; mean ± SD stimulus intensity, 67% ± 21%). Three patients were administered bilateral ECT after 3 to 11 unilateral administrations at a stimulus intensity of 30% to 100% (mean ± SD, 61% ± 14.5%). Antidepressive medication treatment had been discontinued a mean ± SD of 8 ± 4 days before the start of ECT. Because effects of the anesthesia on the metabolite concentrations are possible but unknown, the MRSI measurements were performed at least 30 hours after ECT to avoid such effects on the metabolite concentrations.

MRSI PROTOCOL

Patient compliance was a crucial point in this study: more than 50% of the patients undergoing ECT refused participation in the additional MRSI studies. The main reasons were claustrophobia, problems with lying motionless in the supine position for 40 minutes, or paranoid symptoms related to the investigation. At least 2 data sets were acquired from each patient: one before ECT started and a second after 5 or more ECT treatments within 30 hours to 10 days after ECT. All 1H MRSI studies were performed on a 1.5-T Siemens Vision MRI/MRS system (Erlangen, Germany) equipped with a standard head coil. For MRSI localization, 2-dimensional, fast low-angle shot (FLASH) images in coronal, sagittal, and oblique transverse orientations were obtained. 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.

RESULTS

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 preselection was performed parallel to the transverse images and included both hippocampi. 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. 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. Per data set, mean values of spectra from the left and right hippocampus are reported and added spectrally.

CHANGES INDUCED BY ECT

Five control subjects were studied twice or more approximately 40 minutes, including setup time and acquisition of 1 MRSI data set.

All statistical analyses were performed using statistical software (SPSS for Windows, release 8.0.0; SPSS Inc, Chicago, Ill). The metabolite signals (NAA, Cr, and Ch) of healthy controls were tested for age-related effects using Spearman ρ correlation coefficients, and a linear regression analysis was used for age correction.

Two-tailed, paired t tests were applied to evaluate significant changes of the metabolite signals from repeated MRSI measurements in the same individual. For between-group analysis of the metabolite signals, a general linear model with Tukey post hoc analysis for multiple comparison for the observed means was used. Treatment group was the between-subject factor. The control metabolite signals were also tested within this model for significant sex differences, with sex as the between-subject factor. Statistical significance was evaluated at the $P = .05$ level using 2-sided tests. Data are given as mean ± SD.

STATISTICAL ANALYSIS

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.

Comparison of summed spectra from the hippocampal region before and after ECT shows obvious changes in the relative intensity ratio between NAA and Ch signals, as illustrated in Figure 1, A and B, for the spectra obtained from a patient undergoing ECT.

A 2-tailed paired t test for metabolite signals before vs after ECT revealed that NAA was unchanged (11.4 ± 1.3 vs 11.8 ± 0.9; $t_{10} = −1.8$, $P = .10$), Cr was slightly increased (7.2 ± 0.8 vs 7.7 ± 1.1; $t_{10} = −2.2$, $P = .04$), and Ch was substantially increased (7.9 ± 0.8 vs 9.1 ± 0.9; $t_{10} = −6.0$, $P < .001$).

The mean intraindividual Ch increase was 15.9% ± 11.8%, with a maximum of 39.5%. Despite the mostly unilateral ECT application (14 of 17 patients), the Ch increase was observed bilaterally. The plot of individual Ch signals before and after ECT in Figure 2 shows that in all but 1 patient the Ch signal increased during ECT.

For between-group analysis of intraindividual metabolite signal changes, the differences $\Delta$NAA, $\Delta$Cr, and $\Delta$Ch 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 (F 1,20 =1.17, P =.29) and ΔCr (F 1,20 =0.34, P =.56) but a highly significant difference for ΔCh (ΔChECT=1.20±0.82 and ΔChcontrols =−0.08±0.90; F 1,20 =9.02, P =.007). The Tukey correction for multiple comparisons revealed a substantially different Ch signal 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: F 2,44 =1.39, P =.26; Cr: F 2,44 =0.64, P =.53; and Ch: F 2,44 =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 boxplots 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,32-35 but the direction of the changes is controversial. In addition, results of our study confirm the age-related increase previously reported36 for choline in in vivo proton MR spectra. The fact that NAA remains stable before ECT and remitted patients treated with amitriptyline (P <.001 for both).

For between-group analysis of the metabolite signals, a general linear model with Tukey correction for multiple comparisons was used. Dependent variables were the metabolite signals and the between-subject factor was treatment group (ECT group, n=17; amitriptyline group, n=6; and healthy control group, n=24).

No significant differences were found for NAA (F 2,44 =2.58, P =.09) and Cr (F 2,44 =2.87, P =.07).

A significant group difference was found for the age-corrected Ch signal (Ch before ECT =−1.35±0.78, Ch amitriptyline=0.41±1.02, Ch controls=−0.00±0.64; F 2,44 =20.88, P <.001). 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).

**IS Ch DECREASED BEFORE ECT OR INCREASED AFTER ECT?**

For between-group analysis of the metabolite signals, a general linear model with Tukey correction for multiple comparisons was used. Dependent variables were the metabolite signals and the between-subject factor was treatment group (ECT group, n=17; amitriptyline group, n=6; and healthy control group, n=24).

No significant differences were found for NAA (F 2,44 =1.17, P =.29) and Cr (F 2,44 =3.31, P =.012) but a highly significant difference for ΔCh (ΔChECT=1.20±0.82 and ΔChcontrols =−0.08±0.90; F 1,20 =9.02, P =.007).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ECT Patients (n = 17)</th>
<th>Amitriptyline-Treated Patients (n = 6)</th>
<th>Healthy Control Subjects (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.28 (13.42)</td>
<td>49.67 (13.37)</td>
<td>35.33 (11.64)</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>10/7</td>
<td>2/4</td>
<td>12/12</td>
</tr>
<tr>
<td>ECT treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10.67 (3.68)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Unilateral No.</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Unilateral and bilateral No.</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MRSI measurements, No.</td>
<td>3.44 (1.58)</td>
<td>1.50 (1.22)</td>
<td>1.21 (0.41)</td>
</tr>
<tr>
<td>HAM-D score before ECT</td>
<td>27.67 (4.93)</td>
<td>26.83 (3.31)</td>
<td>NA</td>
</tr>
<tr>
<td>HAM-D score after ECT</td>
<td>7.39 (2.93)</td>
<td>3.83 (2.40)</td>
<td>NA</td>
</tr>
<tr>
<td>Age at onset of depression, y</td>
<td>45.24 (15.65)</td>
<td>45.00 (13.37)</td>
<td>NA</td>
</tr>
<tr>
<td>Episodes of depression, No.</td>
<td>4.78 (5.42)</td>
<td>1.67 (0.52)</td>
<td>NA</td>
</tr>
<tr>
<td>Illness duration, mo</td>
<td>11.34 (15.94)</td>
<td>6.75 (7.35)</td>
<td>NA</td>
</tr>
<tr>
<td>Presence of suicidality</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>2†</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Previous medication use, No.</td>
<td>15</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Tricyclic and tetracyclic antidepressants</td>
<td>17</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>13</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Serotonin and norepinephrine reuptake inhibitors</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Typical antipsychotics</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lithium</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Valproate</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD) unless otherwise indicated. ECT indicates electroconvulsive therapy; NA, not applicable; MRSI, magnetic resonance spectroscopic imaging; and HAM-D, Hamilton Depression Rating Scale.
†One patient started to drink 3 to 4 drinks per day 6 months before ECT and discontinued drinking 2 weeks before ECT started. In a second patient, a diagnosis of alcohol abuse was given 1 year before ECT but could not be confirmed later.
The MRSI-detectable Ch signal represents the quaternary N-methyl groups of a variety of Ch. The MRSI resonance is composed of acetycholine, phosphocholine, glycerophosphocholine, and free choline. Most of the signal arises from phosphocholine and glycerophosphocholine, free choline is less than 5%, and the contribution from acetycholine 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 $^1$H 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 T$_2$ relaxation. This is unlikely because it would necessitate an increase in the Ch T$_1$ relaxation time by a factor of 2.2 to account for a 25% signal increase, assuming a normal T$_1$ 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 $^1$H MRSI, and, hence, spatial resolution is poor and measurement time is prolonged.

Several authors$^{8-10}$ 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$^8$ 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$^{37,38}$ 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.$^{39,40}$ In one study,$^{41}$ 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$^9$ and Gombos et al$^{10}$ reported that long-term administration of ECT induces sprouting of the granule cell mossy fiber pathway in the hippocampus in ani-
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 al concluded 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 al 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.

Accepted for publication May 15, 2000.

This work was supported by Forschungsfond der Universitaet Heidelberg/Manheim 2016, Mannheim, Germany.


We thank Norbert Schuff, PhD, for providing the spherical k-space sampling MRSI sequences; Andrew Maudsley, PhD, and Brian Soher, PhD, for providing the automated spectral fitting routine; Petra Hubrich-Ungureanu, MD, and Thomas Obergriesser, MD, for assistance with patient demographic data; and Bertram Krumm, PhD, for assistance with the statistical evaluation.

Reprints: Fritz A. Henn, MD, PhD, NMR Research in Psychiatry, Central Institute of Mental Health, Postfach 1221 20, D-68072 Mannheim, Germany (e-mail: henn@us200.zi-mannheim.de).

REFERENCES


