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ORIGINAL PAPER

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Subcortical and medial temporal MR-detectable metabolite abnormalities in unipolar major depression

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Abstract The purpose of the present study was to determine whether MR-detectable alterations of choline-containing compounds in two key neural systems involved in major depression disorder namely the hippocampus and the basal ganglia can be detected. Multislice proton magnetic resonance spectroscopic imaging was applied in 11 patients with major depressive disorder (MDD) and ten matched healthy subjects. Voxels were selected from the left and right side of the hippocampus and the putamen. Significantly lower choline-containing compounds in the hippocampus and significantly higher choline-containing compounds in the putamen of patients with MDD compared to healthy subjects were found. No significant differences were found for the other metabolites in the two regions evaluated. Abnormal levels of choline-containing compounds most likely reflect altered membrane phospholipid metabolism. A reduced level in the hippocampus and an increased level in the putamen suggest regionally opponent membrane abnormalities.

Key words major depressive disorder · choline-containing compounds · MR spectroscopic imaging · hippocampus · putamen

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Introduction

Mood-congruent processing biases are amongst the most robust research findings in neuropsychological studies of major depressive disorder (MDD). Functional MR studies could demonstrate increased and decreased activity in depressed patients compared to healthy controls as a response to emotional stimuli [2].

The hippocampus is the focus for hypotheses related to stress and its effects. A reduced hippocampal serotonergic neurotransmission and impaired neurogenesis and synaptogenesis in this brain region have been reported for MDD [4, 8, 9, 14]. We previously observed a decreased signal of MR-detectable hippocampal choline-containing compounds in patients with medication refractory MDD [5].

The basal ganglia are a complex of deep nuclei that consist of the corpus striatum, globus pallidus, and substantia nigra. The corpus striatum, which includes the caudate nucleus and the putamen, receives input from the cerebral cortex and the thalamus and, in turn, projects to the globus pallidus. The basal ganglia are not only involved in motor functions but also have important cognitive, oculomotor, and limbic processing functions. They form a part of the brain neuroanatomic circuits that may be involved in mood regulation and have been increasingly implicated in the pathophysiology of MDD [7, 10].

MRI and PET studies found the hippocampi and the basal ganglia morphologically and functionally altered in MDD compared to healthy subjects. For a review see Ende et al. [7]. In three previous MRS/MRSI studies of the basal ganglia in MDD controversial results have been reported regarding the ratio of Cho to total creatine (tCr). While Renshaw et al. [13] in a single voxel study and a fairly large patient

Table 1 Summary of patient and control characteristics, mean MRSI metabolite values and standard deviations for the hippocampus and putamen

Mean values ± SD	Controls (n = 10; 4 male)	Patients (n = 11; 3 male)
Age	41.0 ± 12.2	44.9 ± 11.1
Beck Depression Inventory	4.8 ± 7.2	23 ± 13.3[b]
$HAMD_{21}$		22 ± 2.3[c]
Hippocampus	(n = 8)	(n = 8)
NAA	6.3 ± 1.2	5.8 ± 0.9
tCr	3.6 ± 0.9	3.1 ± 0.6
Cho	*3.6 ± 1.0*	*3.0 ± 0.6*[a]
GM voxel content	66.4 ± 5.9	61.1 ± 7.3
CSF voxel content	10.4 ± 5.8	8.8 ± 2.8
Putamen	(n = 6)	(n = 8)
NAA	5.7 ± 0.8	6.4 ± 1.0
tCr	2.6 ± 0.3	3.0 ± 0.4
Cho	*2.5 ± 0.4*	*3.0 ± 0.5*[a]
GM voxel content	37.6 ± 14.8	42.9 ± 10.9
CSF voxel content	2.0 ± 0.9	2.5 ± 0.9

[a] $P < 0.05$
[b] Beck Depression Inventory at time of MRSI scan
[c] Hamilton Depression Score (21 items) at time of admission

group (n = 42) reported decreased Cho/tCr, Vythilingam et al. [17] in a recent MRSI study of 17 MDD patients and an early single voxel study by Charles et al. [1] reported increased Cho/tCr in a group of 7 MDD patients compared to controls.

Our proton MRSI study aimed to corroborate reported alterations in MR-detectable choline-containing compounds in depressed patients compared to healthy controls in these two neural key regions of MDD. We hypothesized that Cho would be found decreased in the hippocampus in MDD patients, whereas basal ganglia Cho would show an opposite alteration in comparison to healthy controls.

With the long echo multislice MR spectroscopic imaging method used, spectra with non-overlapping resonances of for *N*-acetylasparte (NAA), a marker of neuronal function, choline-containing compounds (Cho), possibly involved in membrane and myelin sheath metabolism and creatine- and phosphocreatine (tCr) reflecting cerebral energy metabolism were acquired and semi-quantitative measures obtained.

Methods

Eleven inpatients diagnosed for MDD and ten healthy comparison subjects were studied with ^{1}H MRSI. All patients satisfied DSM IV criteria for MDD and were inpatients of the Department of Psychiatry and Psychotherapy at the time of the examination. All patients were on antidepressive medication and no restrictions were made regarding antidepressive co-medication like lorazepam. A summary of patient and control characteristics is given in the Table 1.

After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the university ethics committee.

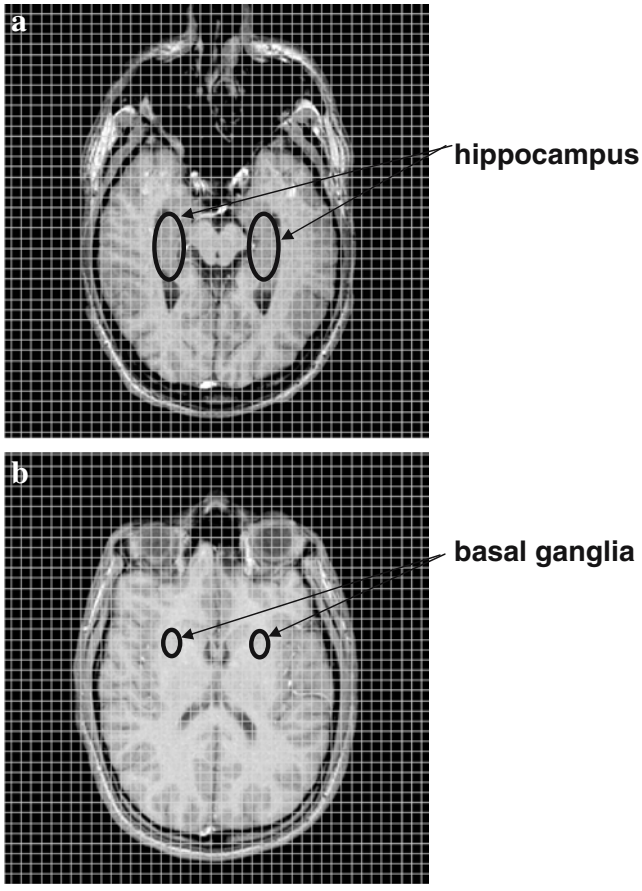

Fig. 1 The location of the MRSI slices and the typical voxel position for the evaluated subregions: (**a**) hippocampi and (**b**) putamen

MRI/^{1}H MRSI examination

All MRSI studies were performed on a 1.5 T Siemens Vision system using a standard CP head coil (Magnetom VISION, Siemens, Erlangen, Germany). Three MRSI slices were acquired within one measurement. A selective lipid inversion pulse, TR = 1,500 ms, TE = 135 ms, FOV = 300 mm, grid = 36 × 36, Slice thickness = 15 mm, nominal voxel size = 1.04 cm^3 (0.8 × 0.8 × 1.5 cm) were used. In addition, a 3D magnetization prepared rapid gradient echo (MPRAGE) data set was acquired.

MRI/^{1}H MRSI co-analysis

Postprocessing of the MRSI data included CSF correction of MRSI brain data to increase sensitivity and decrease variance [18].

Voxels were selected from the left and right hippocampus and left and right putamen. In addition to the metabolite signals the voxel composition for each subregion was evaluated for differences in GM, WM and CSF content. Per data set mean values of spectra from each subregion are reported.

Absolute integral values for NAA, tCr, and Cho were evaluated [6, 11]. In a first analysis all spectra indicated in Fig. 1 were curve fitted. The operator was blinded to the subject's status (patient or control) but not to the research question. The operator chose spectra by anatomical location, at this step blinded to spectral appearance. Spectra were then filtered for further evaluation by objective quality criteria [19]. In a next step these criteria were applied in an automated exclusion routine: linewidth had to be less than 10 Hz, voxel CSF content had to be less than 25%, for hippocampal voxels GM voxel content had to be higher than WM content (Fig. 2).

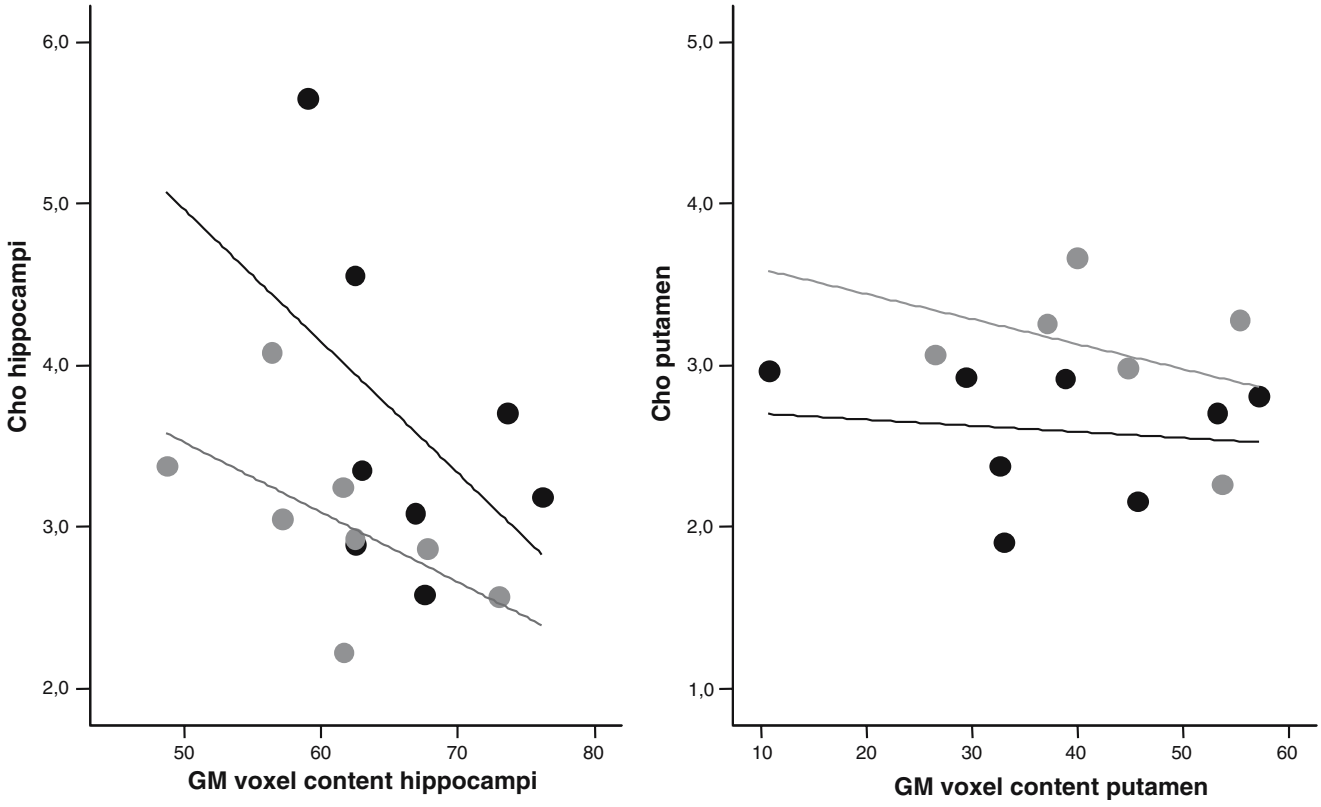

Fig. 2 Scatter plots of the Cho signal in patients (gray circles) and healthy controls (black circles) as a function of voxel GM content

A voxel-based-morphometry (VBM) analysis was performed with SPM2 using the 3D mprage data sets in order to detect morphometrical changes in those brain areas where metabolic changes were hypothesized.

Statistical analysis

Hypothesis driven univariate as well as multivariate analyses based on a general linear model were used for data analysis by the use of SPSS for windows release 12.0. For the univariate analyses the dependent variable was the concentration estimates for Cho in the two subregions (hippocampus, putamen) with group as the between-subject factor and with age and voxel GM content as co-variates. Additionally, according multivariate analyses were conducted with the remaining metabolite measures (NAA, tCr) as dependent variables. We used a paired *t*-test to determine intra-individual left–right metabolite differences. Correlations were assessed with the Spearman's test. The criterion of significance level was set at $P < 0.05$.

Results

The quality criteria based on spectral resolution (spectral linewidth and voxel CSF content) were not met by all spectra from all subjects. Therefore, the group sizes for each evaluated region are less than the total group of acquired data sets (see Table 1). We could not detect a significant left–right hemisphere difference, neither for the hippocampi nor the putamen in both groups (paired *t*-test $P > 0.16$, $t < 1.5$). GM, WM and CSF voxel contents were not significantly different between patients and controls. A Spearman correlation analyses revealed a significant negative correlation between hippocampal GM and the Cho signal in the patient group ($R = -0.81$, $P = 0.02$).

In concordance with our previous results we could corroborate a decreased Cho value in the hippocampus of patients with major depression ($F = 5.73$, df = 1, 12, $P = 0.034$).

In the spectra from the putamen we see a significant above normal Cho value in the patients compared to controls ($F = 5.66$, df = 1, 10, $P = 0.039$). Statistics on the remaining metabolite signal values in these two regions were above the $P = 0.05$ level (tCr, hippocampus: $F = 3.10$, df = 1, 12, $P = 0.1$; tCr, putamen: $F = 3.11$, df = 1, 10, $P = 0.11$; NAA, hippocampus: $F = 1.35$, df = 1, 12, $P = 0.27$ and NAA, putamen: $F = 2.73$, df = 1, 10, $P = 0.13$). Mean metabolite values, GM and CSF voxel contents are summarized in Table 1.

VBM analysis did not reveal any significant differences in neither hippocampal nor striatal volumina between MDD patients and controls.

Due to the small sample size a co-analysis of medication effects (e.g. dosage or medication type) was not performed.

Discussion

The hippocampus is the focus for hypotheses related to stress and its effects. A reduced hippocampal Cho

signal is in good accordance to reduced serotonergic neurotransmission and impaired neurogenesis/synaptogenesis in this brain region, respectively [8, 9]. We previously observed a decreased Cho signal in the hippocampus in MDD patients [5]. Additionally, two previous MRSI studies of the basal ganglia in major depression reported increased Cho/tCr in the putamen. This is in concordance with our finding of an increased striatal Cho signal with the tCr signal unchanged.

Patients of our earlier study were medication resistant and more severely ill. Their hippocampal Cho levels increased to normal levels with electroconvulsive therapy. Normal choline levels were also observed in remitted patients treated with amitriptyline [5]. Cho decreased again in our 12-month follow-up study without patients necessarily relapsing [12].

Structural or functional abnormalities of the limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit have been reported and are associated with an increased risk for major depression [3]. Smaller hippocampal, caudate and putamen volumes have been reported in several MRI studies of major depression [7]. Functional investigations stated unidirectional alterations in striato-limbic areas. The Danish/PET depression project observed an increased CBF (right sided) in MDD patients in hippocampal and striatal regions [16]. Presentation of sad and happy facial expressions showed fMRI alterations of the same sign in parahippocampal and putaminal regions. A differential pattern of neural response toward sad versus happy facial expressions in MDD was observed by Surguladze et al. [15]. These results do not necessarily contradict MRSI findings of regionally opposed cholinergic changes. It can be speculated, that deficits in hippocampal synaptogenesis as predicted by the neurotrophin hypothesis lead to compensatory functional alterations in other regions within the LCSPT circuit. Striatal synaptic and/or membrane alterations (here: possibly an increased membrane turnover) are then reflected in a detectable Cho rise.

Conclusion

Overall, abnormal Cho signals most likely reflect altered membrane phospholipid metabolism. A reduced level in the hippocampus and an increased level in the putamen suggest regionally opponent membrane abnormalities in MDD.

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