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ORIGINAL PAPER

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Multiregional ^{1}H-MRSI of the hippocampus, thalamus, and basal ganglia in schizophrenia

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Abstract *Background* The hippocampus, thalamus and basal ganglia are among the brain regions of major interest in schizophrenia. *Aims* The purpose of this study was to corroborate previous findings of reduced *N*-acetylaspartate in the hippocampal and thalamic regions and to investigate possible metabolite changes in the putamen in schizophrenia. *Method* MRSI study of the thalamus, basal ganglia, and hippocampus in 13 schizophrenic patients under stable medication and age-matched healthy controls. *Results* A decrease of the *N*-acetylaspartate signal was found in the hippocampal region and the thalamus but not in the putamen of patients compared to controls. No significant group differences in the signals from creatine and phosphocreatine, and choline-containing compounds were found in the hippocampal region and the putamen but the signal from choline-containing compounds was decreased in the thalamus of patients. *Conclusion* Metabolic processes in the basal ganglia of schizophrenic patients seem to be opposite the hippocampal and thalamus findings.

Key words schizophrenia · *N*-acetylaspartate · hippocampus · basal ganglia · putamen

Introduction

Brain abnormalities reported in schizophrenia implicate a variety of interrelated brain regions, primarily the medial temporal, prefrontal, thalamic, and basal ganglia areas (Torrey 2002).

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Magnetic resonance spectroscopic imaging (MRSI) measures relative concentrations of *N*-acetylaspartate (NAA), creatine and phosphocreatine (Cr), and choline-containing compounds (Ch). NAA is regarded as a putative neuronal/axonal marker or functional marker. Cr measures energy metabolism and is supposed to be relatively stable. The Ch signal 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.

It has been proposed that the hippocampus is a potential site for a neurodevelopmental lesion in schizophrenia and various MRSI studies have found decreased NAA values or NAA ratios in the hippocampus of schizophrenic patients (Deicken et al. 1999, 1998; Nasrallah et al. 1994; Bertolino et al. 1998a, 1998b; Maier et al. 1996). The thalamus is involved in the processing of sensory inputs and a variety of interactions among cortical, subcortical and brainstem nuclei (Hazlett et al. 1999). The basal ganglia with the putamen and caudate nuclei is not only involved in motor functions but also has important cognitive, oculomotor, and limbic processing functions (Hokama et al. 1995) all of which are thought to be important in schizophrenia.

The purpose of this study was to investigate whether in schizophrenic patients the reduced NAA in the hippocampal region is accompanied by low NAA in the thalamus and basal ganglia since the hippocampus, the thalamus and the basal ganglia are among the brain regions of major interest in schizophrenia.

Materials and methods

Patients and control subjects

Thirteen patients (8 male, 5 female) satisfying DSM-III-R (American Psychiatric Association, 1987) as well as ICD 10 criteria for schizophrenia who had been diagnosed for at least 24 months participated

in this MRSI study. The age range was 23–47 years (mean age 33.0 ± 7.0 years). All patients had been evaluated at the Central Institute of Mental Health and were clinically stable for at least 6 months and had no medication changes during a period of at least 3 months. Five of the 13 patients received typical neuroleptic medication and had never been on atypical medication, whereas eight patients received atypical medication for at least the last 3 months. Mean illness duration was 131.3 ± 88.3 months with a range of 6 to 285 months. All patients underwent separate structural MRI scans. Qualitative evaluation of the structural images by a neuroradiologist blind to subject status revealed no major structural abnormalities.

Fifteen MRSI data sets of healthy subjects were obtained for control (age range 22–48 years, mean age 31.9 ± 6.7 years). None of the patients and controls had a history of head injury, organic mental disorder, neurological disorder, alcohol or substance abuse. There were no significant group differences between patients and controls for age. Written informed consent was obtained after the purpose of the study and the procedures were explained to all participants. The study was approved by the university ethics committee.

MRSI data acquisition

The MRSI data were acquired on a 1.5 T Magnetom VISION™ (Siemens, Erlangen, Germany) using a standard circularly polarized head coil. For reduced motion of the subject's head, a vacuum-molded head holder (Vac-Pac, Olympic Medical, Seattle, WA) was employed. For localization of the MRSI slices 2D FLASH images in coronal and sagittal orientation were acquired. The oblique transverse images were then planed on these two orthogonal data sets using another FLASH series angulated parallel to the hippocampi and turbo spin echo images for localization of the basal ganglia and thalamus region (parallel AC-PC line on the sagittal image). The transverse FLASH images were angulated parallel to the hippocampi. Two 2D MRSI sequences with PRESS volume selection were used with the volume angulated parallel to the hippocampi and putamen/thalamus, respectively. A MRSI field of view (FOV) of 210 × 210 mm was used with circular k-space sampling equivalent to a maximum of 24 × 24 phase encoding steps (Maudsley et al. 1994). Other measurement parameters included TE = 135 ms and TR = 1.5 s for basal ganglia and thalamus and TR = 1.8 s for the hippocampus resulting in a measurement time of 11 minutes and 13 minutes, respectively. Both MRSI data sets could be acquired within one MR session and total measurement time including localizer images and shimming was about 60 minutes. Figs. 1 and 2 show sagittal and oblique transverse FLASH localizer images with the PRESS MRSI box for the hippocampal area (1) and the basal ganglia and thalamus (2) superimposed. Below the MR images spectra from the hippocampal region, the thalamus and the putamen from a schizophrenic patient, and a healthy control are shown.

MRSI processing

For postprocessing of the MRSI data an automated spectral fitting program was used. This program uses a parametric spectral model with acquisition specific a priori information, in combination with a wavelet-based, nonparametric characterization of baseline signals. A k-space apodization resulting in an effective voxel size of approximately 4 ml and zero filling to 32 × 32 k-space points was applied prior to the spatial Fourier transformation. Zero filling from 512 to 1024 time domain data points and Gaussian multiplication corresponding to 0.6 Hz line broadening were carried out prior to the time domain

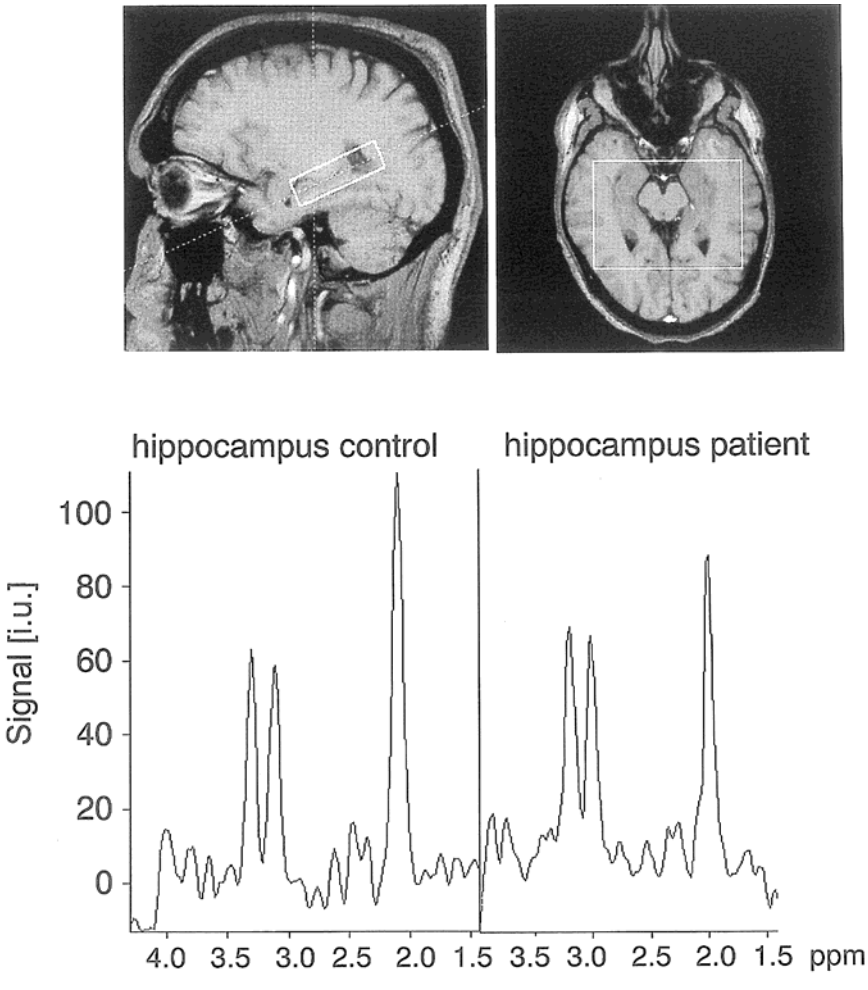


Fig. 1 *Hippocampal region:* sagittal and oblique transverse FLASH localizer images with the PRESS MRSI box superimposed and representative spectra from a schizophrenic patient and a healthy control

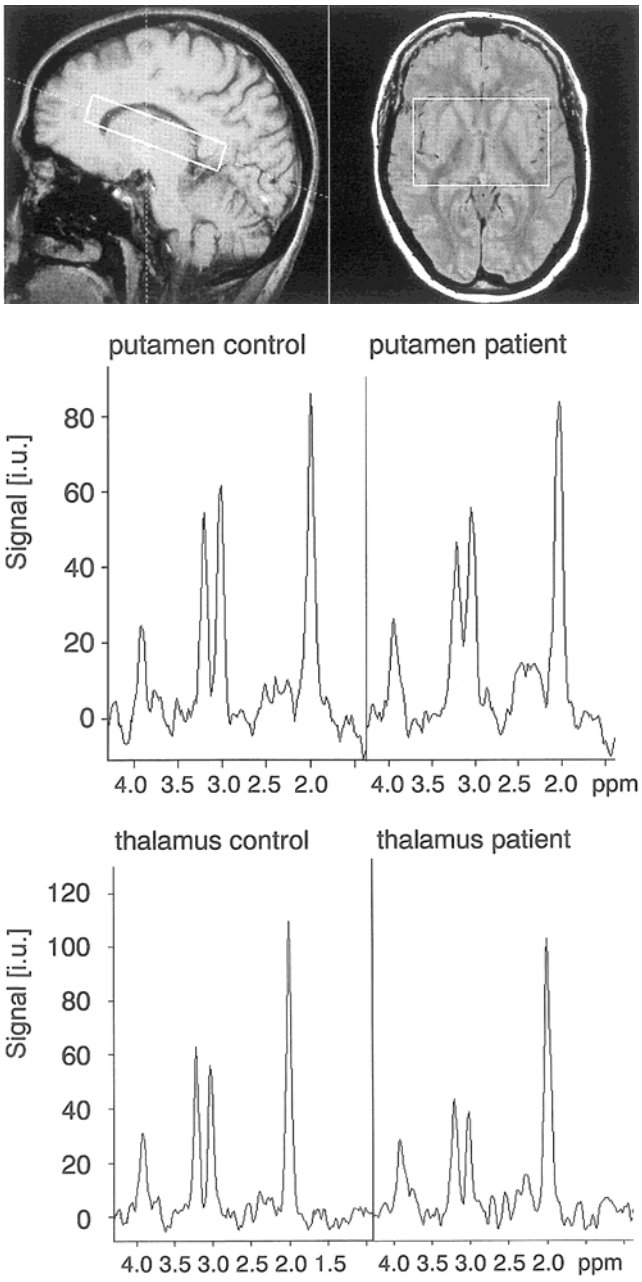


Fig. 2 *Thalamus and basal ganglia:* sagittal and oblique transverse FLASH localizer images with the PRESS MRSI box superimposed and representative spectra from a schizophrenic patient and a healthy control

Fourier transformation. Spectral phasing was also performed automatically. The signals of NAA, Cr, and Ch were curve fit and voxels from left and right hippocampus, putamen and thalamus were manually selected. Following the voxel selection introduced by Deicken et al. (2000), one voxel from each side of the thalamus was selected from the mediodorsal thalamic region. Voxels with linewidths above 10 Hz have been excluded from further analysis.

Mean values of spectra from each region are reported and added spectra are shown in Figs. 1 and 2. Absolute integral values for NAA, Cr, and Ch were corrected for differential head coil loading by multiplication with the transmitter reference voltage (Ende et al. 2000, Obergriesser et al. 2001). This yields a semi-quantitative measure and thus absolute metabolite values can be compared in addition to metabolite ratios.

Statistical analysis

Multivariate analysis based on a general linear model was used for data analysis by the use of SPSS for windows release 10.0. The dependent variable was the concentration estimate for each metabolite (NAA, Cr, or Ch) and group was the between-subject factor. A paired t-test was used for comparison of regions within the same data set. Statistical significance was evaluated at the 0.05 level.

Results

Hippocampus

As expected, significantly decreased metabolite signals in the hippocampi were found for NAA ($F = 9.9$, $df = 1,26$, $p = 0.004$), but not for Cr and Ch in patients relative to controls ($p > 0.7$). NAA/(Cr + Ch) ratios were also significantly lower in patients than controls ($F = 8.0$, $df = 1,26$, $p = 0.009$). Illness duration did not correlate significantly with the NAA signals ($r = -0.04$, $p > 0.4$).

Basal ganglia

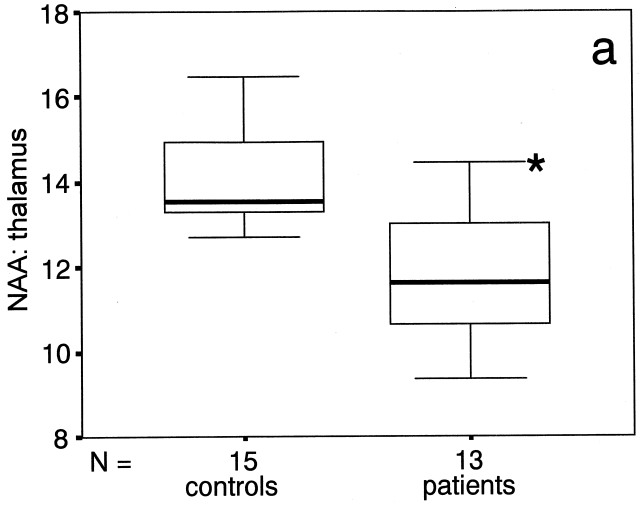
Spectral resolution in the caudate nuclei area was poor due to partial volume effects. Therefore, only spectra from the putamen could be evaluated. All three metabolite signals and the NAA/(Cr + Ch) ratios from the putamen did not differ significantly between patients and controls ($F < 1.7$, $df = 1,26$, $p > 0.2$). Illness duration did not correlate significantly with the NAA signals ($r = -0.4$, $p > 0.1$).

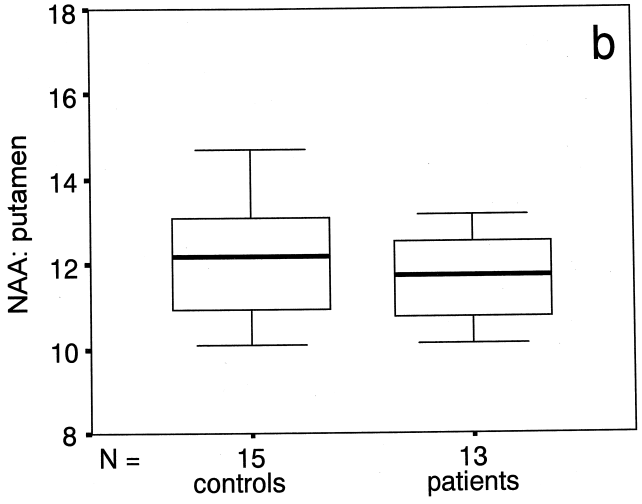
Thalamus

Following the voxel selection introduced by Deicken et al. (2000), we found significant lower metabolite signals for NAA ($F = 21.5$, $df = 1,26$, $p = 0.00007$), and Ch ($F = 9.6$, $df = 1,26$, $p = 0.004$) in patients relative to controls (Ende et al. 2001). The Cr signal was unchanged ($F = 2.6$, $df = 1,26$, $p = 0.121$). The NAA/(Cr + Ch) ratio was not significantly different between the groups ($F = 2.9$, $df = 1,26$, $p = 0.102$). Illness duration did not correlate significantly with the NAA signals ($r = 0.1$, $p = 0.4$).

Boxplots for NAA and Ch from all three brain regions evaluated are shown in Figs. 3 and 4. The mean MRSI metabolite values and standard deviations for these brain regions are summarized in Table 1.

No significant correlation between the NAA, Cr or Ch signal and age was found for patients and controls in any of the investigated brain regions. Only the hippocampal region showed a *trend* for NAA to decrease and Ch to increase with age.





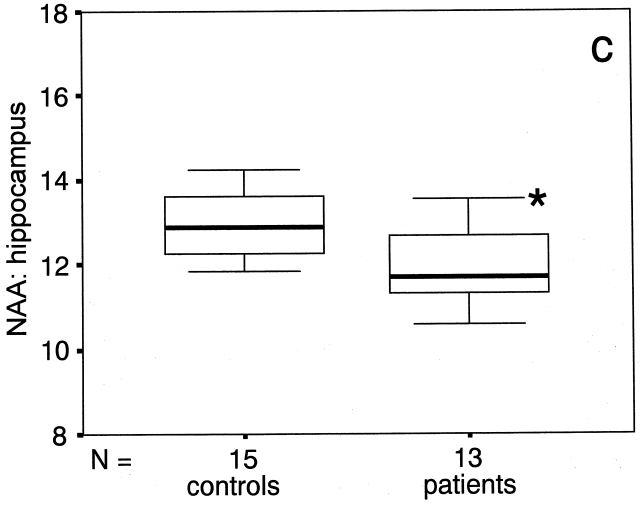
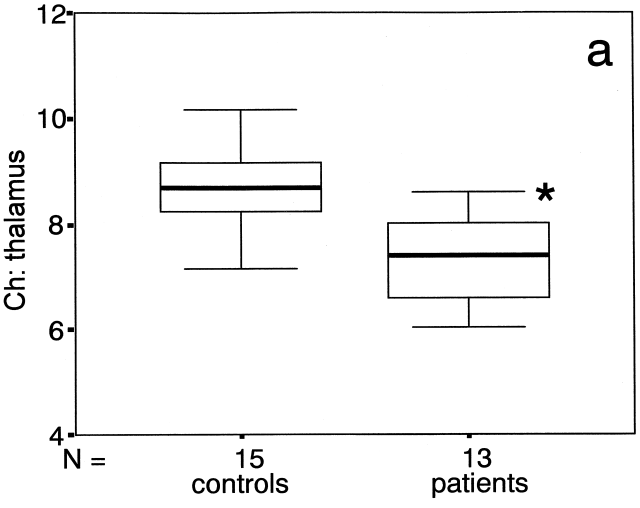
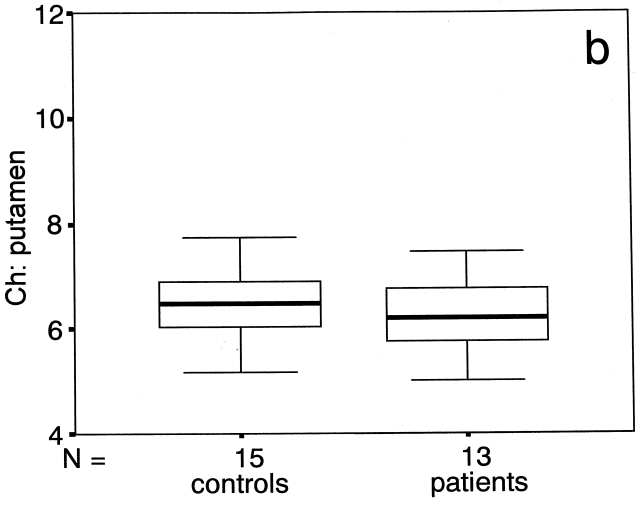


Fig. 3 *NAA distribution:* boxplots for NAA signals in patients and controls: **a** thalamus, **b** putamen, **c** hippocampus. Asterisks indicate $p < 0.05$





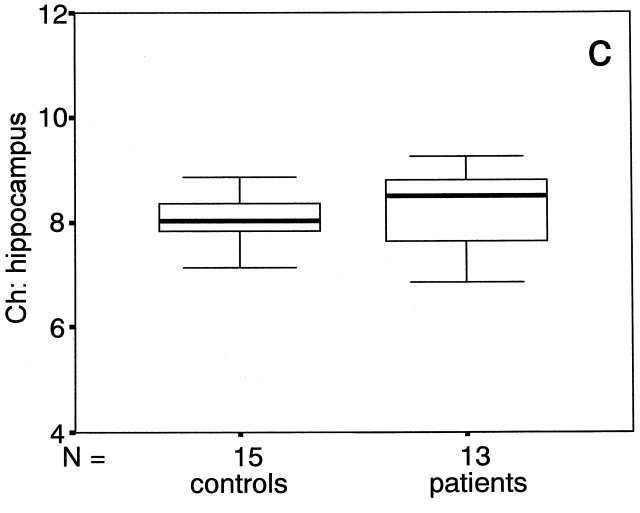


Fig. 4 *Ch distribution:* boxplots for Ch signals in patients and controls: **a** thalamus, **b** putamen, **c** hippocampus. Asterisks indicate $p < 0.05$

Table 1 Mean MRSI metabolite values and standard deviations for the evaluated three brain regions

Mean values ± SD	Controls (n = 15)	Patients (n = 13)
Age	31.9±6.7	33.0±7.0
Illness duration (months)	–	131.3±88.3
Hippocampus NAA	12.9±0.8	11.8±1.0[a]
Hippocampus Cr	7.3±0.6	7.3±0.5
Hippocampus Ch	8.1±0.7	8.2±0.8
Hip. NAA/(Cr + Ch)	0.84±0.06	0.77±0.07[a]
Thalamus NAA	14.3±1.4	11.9±1.5[a]
Thalamus Cr	6.8±0.7	6.4±0.7
Thalamus Ch	8.6±1.1	7.5±0.9[b]
Thal. NAA/(Cr + Ch)	0.94±0.12	0.87±0.13
Putamen NAA	12.1±1.4	11.7±1.1
Putamen Cr	7.5±0.9	7.1±0.6
Putamen Ch	6.5±1.0	6.3±0.7
Put. NAA/(Cr + Ch)	0.87±0.09	0.89±0.11

[a] Anova: $p < 0.01$; [b] Anova: $p < 0.05$

Discussion

Hippocampus

Our study confirms the previous findings of a decreased NAA signal in the hippocampus in schizophrenia compared to healthy controls (Deicken et al. 1998, 1999; Nasrallah et al. 1994; Bertolino et al. 1998a, 1998b; Maier et al. 1996; Deicken et al. 2000; Ende et al. 2001). The results of MRI studies on structural anomalies like hippocampal volume reductions or asymmetry are the most clear and prominent features in schizophrenia (Harrison 1999; Wright et al. 2000; Okugawa 2001). The repeated finding of reduced NAA in the hippocampus in the absence of significant changes of the Ch signal could be explained as selective neuronal loss without increased membrane turnover. It is consistent with a process like neuronal apoptosis which does not elicit reactive gliosis. But repeated findings of reduced NAA in the absence of volumetric changes (Deicken et al. 1999; Bertolino et al. 1998a, 1998b) suggest that NAA may be measuring neuronal dysfunction rather than neuronal loss.

Thalamus

Whereas MRSI results for hippocampal NAA in schizophrenic patients are mostly concordant, discordant findings in the thalamus have been previously reported (Omori et al. 2000; Deicken et al. 2000; Bertolino et al. 1996, 1998b; Heimberg et al. 1998; Delamillieure et al. 2000). MR imaging and PET data on structural and functional alterations of the thalamus also revealed controversial results (Hazlett et al. 1999 (and references within); Andreasen et al. 1999; Corson et al. 1999; McCarley et al. 1999). The results of a study combining high resolution MRI with functional PET measurements (Hazlett et al. 1999) point out that morphologic changes of the thalamus in schizophrenia are only marginal but there are pronounced functional changes very localized to subregions of the thalamus, most pronounced in the mediodorsal nucleus. Whereas Omori et al. (2000) and Deicken et al. (2000) found a significant bilateral reduction in the thalamus of the NAA signal and ratio, Bertolino et al. (1996, 1998b) and Delamillieure et al. (2000) did not find significant differences between schizophrenic patients and controls in the thalamus. In a single voxel study, Heimberg et al. (1998) found a trend towards reduced NAA in the left thalamus. Deicken et al. (2000) reported a decreased NAA signal in the mediodorsal region of the thalamus in schizophrenic patients. The authors pointed out that the discrepancy between their findings and previous MRSI studies (Bertolino et al. 1996, 1998b) may be the result of differences in voxel selection. We could corroborate the finding of decreased NAA in the selected voxels of the mediodorsal region of the thalamus in schizophrenic patients (Ende et al. 2001).

These results are accompanied by the less pronounced but still significant finding of simultaneous decrease of the Ch signal in this region. The interpretation of this finding is complicated by the fact that the choline resonance represents signals from several choline containing compounds, all with different functional roles. Low choline gives evidence for a lack of gliosis and supports the hypothesis of a neurodevelopmental disturbance with less connectivity in the mediodorsal nucleus of schizophrenic patients.

Putamen

In contrast to other brain regions investigated in schizophrenic patients, the volumetric studies of the basal ganglia show an increase rather than a decrease in the patients compared to controls (Elkashef et al. 1994; McCarley et al. 1999). Functional and metabolic processes in the basal ganglia seem to contradict hippocampal and thalamus findings. Several studies report proton MR spectroscopy investigations of the basal ganglia region in schizophrenia (Fujimoto et al. 1996; Sharma et al. 1992; Heimberg et al. 1998; Shioiri et al. 1996; Block et al. 2000; Bustillo et al. 2001) with discordant findings. The study by Fujimoto et al. (1996) is the only study reporting bilaterally decreased NAA/Ch ratios. Block et al. (2000) and Bustillo et al. (2001) could not find metabolic abnormalities in the basal ganglia. Significant unilaterally (left) increased Ch signals in the basal ganglia of schizophrenic patients were found by Fujimoto et al. (1996) and Shiori et al. (1996), whereas Heimberg et al. (1998) report decreased levels of the Ch signal in the left basal ganglia.

Buchsbaum et al. (1997) pointed out that, in contrast to other brain regions, the basal ganglia in schizophrenia may show an atypical pattern of volumetric and

metabolite changes over time. McCarley et al. (1999) review that two thirds of the voluming studies in schizophrenia report positive findings for basal ganglia volumes with a trend of increased volume in patients treated with typical neuroleptics.

In a previous MRSI study of the anterior cingulate region in schizophrenic patients, we found that only the group of patients treated with typical medication had a significant reduction in NAA compared to the controls (Ende et al. 2000). It seems likely that there might also be an effect of neuroleptic drugs on the NAA metabolism in the thalamus and hippocampus. Unfortunately, our sample size of only 5 patients under typical medication is too small for valid statistical evaluation. Nevertheless we see similar trends towards a lower NAA signal in patients under typical neuroleptica in both regions. Larger patient groups will be needed to corroborate these preliminary findings.

Another confining aspect of this study is that only patients with chronic schizophrenia were studied in a cross-sectional design. Volume MRI data of the patients and controls have not been used for tissue segmentation and CSF correction of the MRSI data.

Overall, reduced NAA as a sign for abnormalities in neuronal function and viability can be demonstrated in the hippocampus and thalamus opposed to that in the putamen suggesting that there is a selective involvement of particular brain regions in schizophrenia.

The findings are consistent with a neurodevelopmental process in schizophrenia.

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