The centre médian-parafascicular complex of the thalamus in schizophrenia - a morphometric postmortem study

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Introduction

- Evidence from neuropathological (Pakkenberg 1992, Danos et al 2002, 2003, Byne et al 2002, Highley et al 2003) and MRI studies (Andreasen et al 1998, Byne et al 2001) indicate structural alterations of the thalamus in schizophrenia.
- The CM-Pf complex is reciprocally connected with the basal ganglia (Parent et al 2001) which are known to be involved in the antipsychotic effects of neuroleptics. The CM-Pf complex projects also to various cortical areas, but the main output leads to the striatum.
- On a functional level, the CM-Pf complex is involved in attentional processes (Matsumoto et al 2001).
- A recent postmortem study reported no significant volume alterations of the centromedian nucleus (Byne et al 2002). However, this study has no examined the whole céntremdian-parafascicular complex.
- The aim of the present study was the assessment of the volume of the CM-Pf complex in the brains of schizophrenia patients and normal controls.

Subjects

•Post-mortem brain tissue of 8 patients with schizophrenia according to DSM-III-R (6 males, 2 females, mean age=51,5 years) and 12 matched normal control subjects (7 males, 5 females, mean age=55,2 years) were used for the present study. All brains were obtained from the new Magdeburg brain collection. Patients and normal controls died between the years 1986 and 1993. Age ranged from 38 to 65 years.

•A lifetime psychiatric diagnosis of schizophrenia was established according to DSM-III-R by All subjects with schizophrenia had histories of inpatient hospitalization. The mean duration of illness was 19.3± 7.7 (mean ± SD) years.

•Control brains without a history of neuropsychiatric disorders were obtained from the same pathological institutes, or medical examiner's officers. Brains with life-time reports of abuse of alcohol or drugs, dementia, neurological illness, trauma, chronic terminal diseases known to affect the brain (i.e. chronic liver, kidney, heart and lung diseases, cancer, cortisol treatment) were excluded.

•All patients had received antipsychotic medication with neuroleptics during the course of their disease. Six of the patients were chronically treated with typical neuroleptics, one patient was treated with clozapine, in one patient the precise neuroleptic dose is not available. The cumulative dose of neuroleptic medication for the last two years of therapy was calculated. The mean (± SD) dose in chlorpromazine equivalents was 6.8×10^5 ($\pm 4.2 \times 10^5$) mg.

Morphometric analysis

•Brains were removed within 24 to 48 hours after death. After embedding of all parts of the brains in paraffin, serial coronal sections of the middle block were cut at 20 mm on a microtome. Every 50th section received a combined staining of Nissl's (cresyl violet) and myelin (Heidenhain-Wölcke or Luxol fast blue). Thus, the distance between these stained sections was 1 mm.

•The perimeters of the medial pulvinar (CM-Pf complex) were delineated on each section in which they were present (Fig. 1). Since the boundaries between CM and Pf are interdigitated without sharp transitions (Heinsen et al 1996) and because the most pallidal projections to CM innervate also the Pf (Parent et al 2001), we descided to estimate the volume of both nuclei and use the term centre médian-parafascicular complex. The boundaries of the CM-Pf complex were delineated under a microscope at low magnification with a 2.5 x objective according to the cyto- and myeloarchitectonic criteria of Morel et al (1997). Volumes were then calculated from areas measured performing morphometric operations. To establish interrater reliability (intraclass correlation), repeated measurements for 8 randomly selected brains were carried out by two tracers (P.D., R.S.) for all investigated nuclei. The interrater reliability (intraclass correlation) was 0.84.

•Whole brain volumewas calculated using the fresh whole brain weight and the brain density coefficient

Statistical analysis

•Student's t tests and a chi-square test were used to compare the schizophrenia group and the control group on demographic data, potential confounding factors and differences in the right and left CM-Pf volume. The statistical significance was set at P<.05.

•A stepwise multiple regression analysis was performed to control for the possible influence of age, post-mortem interval, fixation interval, whole brain volume on the of right and left CM-Pf complex. Pearson correlations were calculated between the length of illness and the volume of the right and left CM-Pf complex. For the stepwise multiple regression analysis, the statistical significance was Bonferroni- corrected due to the multiple comparisons problem.

• For the analysis of possible lateralization effects, an asymmetry coefficient was calculated: Laterality quotient=((Left-Right)/(Left+Right)) x 100

Confounding variables

•Student's t tests (age, postmortem interval, fixation interval, whole brain volume) and a chi-square test (gender) were used to compare the schizophrenia group and the control group on demographic data and potential confounding factors. There were no significant differences between patients with schizophrenia and controls in following potential confounding variables (mean S.D.): age (patients with schizophrenia= 51.5 ± 5.7 years, normal controls= 55.2 ± 8.9 years, P=0.30), gender (patients with schizophrenia= 6 males, 2 females; normal controls= 7 males, 5 females; P=0.64), whole brain volume (patients with schizophrenia= 1328 ± 73 cm^3, normal controls = 1254 ± 141 cm^3, P=0.21), fixation interval (patients with schizophrenia=6.9 ± 2.8 months, normal controls= 8.0 ± 5.4 months, P=0.60) and post-mortem interval (patients with schizophrenia= 39.0 ± 12.4 hours, normal controls= 31.6 ± 14,6 hours, P=0.26).

•A stepwise multiple regression analysis was performed to control for the possible influence of age, post-mortem interval, fixation interval, whole brain volume on the of right and left CM-Pf complex. The correlation factors for each of potential confounding variables were without significance.

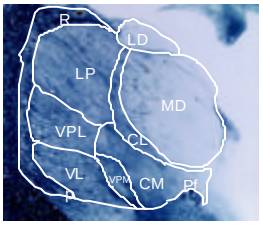

Fig. 1. Photomicrograph of a Nissl-myelin stained coronal section through the human thalamus at the level of the centre médian-parafascicular complex (bar= 2 mm). Abbrevations: CM= Centre médian nucl, CL=Central lateral nucl, LP=Lateral posterior nucl, MD= Mediodorsal nucl, Pf=Parafascicular nucl, R=Reticular nucl, VLp=Ventral lateral posterior nucl, VPL= Ventral posterior lateral nucl, VPM=Ventral posterior medial nucl.

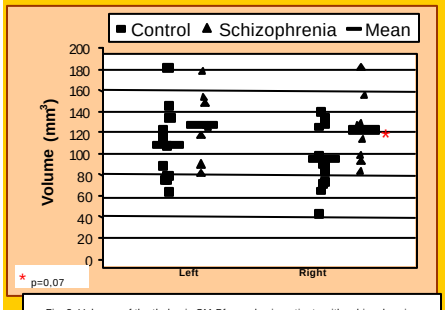

Fig. 2. Volumes of the thalamic CM-Pf complex in patients with schizophrenia and normal controls.

Results

•The whole brain volume was not significantly correlated with the volumes of the right or left CM-Pf complex in both groups (patients or normal controls).

•Patients with schizophrenia exhibited a near-significant (+28.4 %, P=0.07) volume increase of the right CM-Pf complex (Fig.2).

•The volume of the left CM-Pf complex was also increased in the schizophrenia group (+20.0 %, P=0.25), however this difference was not significant.

•There was no significant between-group difference in the laterality quotient.

•The volumes of the right and left CM-Pf complex were not significantly correlated with the cumulative dose of typical neuroleptics, length of illness among the schizophrenia patients.

Discussion

•In a previous postmortem study (Byne et al 2002), no volume difference was found between schizophrenia patients and comparison subjects in the volume of the centromedian nucleus only. However, in the study of Byne et al (2002) only the centromedian nucleus was analyzed, whereas in the present study, the whole céntremedian-parafascicular complex was measured. Furthermore, this study used other anatomical criterias (Ray and Price 1993) for delineation of the centromedian nucleus than the criteria used in the present study (Morel et al 1997).

• Since the CM-Pf complex has strong reciprocal connections with the basal ganglia, our results may be associated with MRI findings of increased basal ganglia volume after treatment with typical neuroleptics (Chakos et al 1994). However, in the present study the volumes of the right and left CM-Pf complex were not significantly correlated with the length of illness, or with the cumulative dose of medication with typical neuroleptics.

•Therefore, it is still unclear whether our finding of an increased volume of the right CM-Pf complex is a consequence of chronic neuroleptic treatment or reflects an intrinsic structural alteration associated with the pathogenesis of schizophrenia.

•We have found the significant volume increase only in the right CM-Pf. However, the laterality coefficient was not significantly altered in the schizophrenia group. Therefore, it is still unclear whether lateralisation plays a relevant role in this finding.

•On the neurophysiological level, recent studies in primates reported that neurons in the CM-Pf complex are supply striatal neurons with alerting stimuli such as unexpected handclaps and noises (Matsumoto et al 2001). Taken together, it appears possible that the structural abnormalities found in the CM-Pf complex may be related with paranoid symptoms experienced by patients with schizophrenia.

Acknowledgements

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