

Volumetric analyses of the mediodorsal thalamus in affective disorders: a postmortem study

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Introduction

- Structural and functional studies found evidence for an involvement of the mediodorsal nucleus of the thalamus (MD) in the pathogenesis of affective disorders (Drevets 2000, Young et al 2004).
- The mediodorsal nucleus (MD) is an association nucleus of the thalamus. It has reciprocal anatomical connections with the prefrontal cortex and the temporal lobe. (Giguere und Goldman-Rakic 1988, Yeterian und Pandya 1991).
- The aim of the present study was the analysis of the volume of the right and left mediodorsal nucleus of the thalamus in patients with an uni-order bipolar affective disorder and in normal controls.
- Since previous studies in the brain stem of patients with an affective disorder (Bielau et al 2005) have found structural differences between patients who committed suicide and patients with other causes of death, we have analyzed these two groups separately.

Subjects

- Brains of 17 patients (10 females, 7 males) with a diagnosis of an affective disease according to DSM-III-R criteria (unipolar n=7, bipolar n=10) were analyzed.
- The mean length of disease was 5.5 years in the group of unipolar patients and 16.6 years in the group of bipolar patients.
- All patients have received psychopharmacological treatment (tricyclic antidepressants, classical neuroleptics, benzodiazepines and lithium).
- The normal control group included 20 age- and gender-matched persons (10 female, 10 male) without neuropsychiatric diseases.
- Exclusion criteria in the normal control group were neurodegenerative diseases, intracerebral tumors, infections, vascular or traumatic diseases, alcohol- or drug abuse.

Tissue processing and sampling

- Brains were removed after death and fixed in toto in 8 % phosphate-buffered formaldehyde for at least 2 months (pH=7.0, T=15-20 °C).
- Frontal and occipital poles were separated by coronal cuts anterior to the genu and posterior to the splenium of the corpus callosum. After embedding of all parts of the brains in paraffin, serial coronal sections of the middle block were cut at 18 micrometer were cut and mounted.
- Every 50th section was stained according to the combined Nissl (cresyl echt violet) and myelin (Heidenhain-Wölcke) procedure.
- The section thickness after the histological procedures was 18.7 microm. Distance between these stained sections was 1 mm. Sampling of the sections was performed systematically, using each stained section for investigation. About 14-16 sections were used for the present study.

Morphometric analyses

- Morphometric analysis was performed by a single observer (S.K.) who was blind to diagnostic and all demographic information. The boundaries of the MD, defined on the basis of cyto- and myeloarchitectonic criteria (Hirai and Jones, 1989) were delineated under a stereomicroscope (Olympus SZX12, Olympus Optical Co., Japan)(magnification, x 2.5 objective).
- The volume of the whole MD including all subnuclei (parvocellular, densocellular, magnocellular) was assessed in the present study. MD is surrounded by the internal medullary lamina anteriorly, ventrally, and laterally. The medial border was easy to delineate since it is near the lateral wall of the third ventricle. The zone within the thalamus between the posterior portion of the MD and the anterior portion of the was more difficult to assess, since posteriorly the internal medullary lamina breaks up into small islands of cells. This region with islands of cells embedded within the internal medullary lamina was regarded as a part of the central lateral nucleus (Hirai and Jones, 1989) and was not included in the MD. Therefore, the confluence of stria medullaris thalami and the fasciculus retroflexus was chosen as an anatomical landmark for the limitation of the posterior portion of the MD.
- The perimeter of the MD was delineated on each section in which they were present. Volumes were calculated from areas measured performing morphometrical operations previously described in detail (Bogerts et al., 1990).

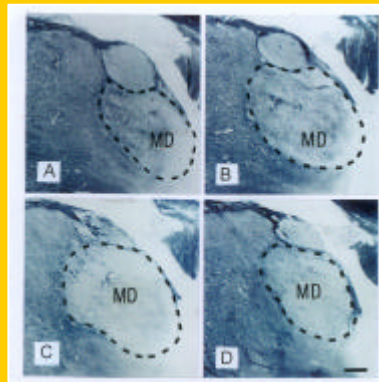


Fig. 1. Frontal slides in antero-posterioren directio at the level of the mediodorsal thalamus (MD). Scale bar=1 mm.

MD – Volume and suicide

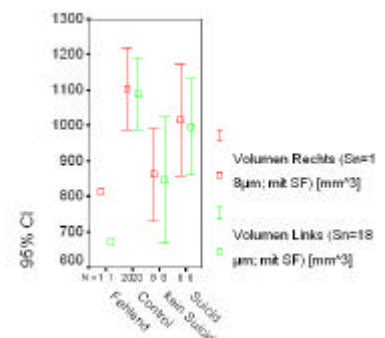


Fig. 2. Volume of the right and left MD in patients with an affective disorder who committed suicide ("Suicid"), in patients with other cause of the death ("kein Suicid") and in normal controls.

Statistical analysis

- The nonparametrical Kolmogorov-Smirnov tests were used to determine whether the thalamic data (volume, neuron density and total neuron number of left and right MD) or potential confounding variables (age, post-mortem interval, fixation interval) were normally distributed. Student's t tests were performed for the comparisons of these confounding variables between the schizophrenia group and the normal control group.
- MD volume was analyzed by three-way ANOVAs with diagnosis and gender as grouping factors and hemisphere (left/right) as repeated measure. Separate ANOVAs were performed for each hemisphere with diagnosis and gender as grouping factors. The possible effect of the whole brain volume on the analyses was investigated by performing a parallel set of ANOVAs for the MD volume.
- For the analysis of possible lateralization effects, asymmetry coefficients were calculated for the volume (Right-Left)/(Right+Left) x 100).
- Separate ANOVAs were used for the asymmetry coefficients with gender and diagnosis as grouping factors; statistical significance was defined at $P < 0.01$ (0.05/4) with Bonferroni corrections for multiple comparisons.
- Pearson's correlation coefficients were performed to examine the possible influence of whole brain volume, age, post-mortem interval, fixation on the MD volume. Pearson's correlations were also performed to examine the influence of the length of illness on the MD volume.
- Statistical analyses were performed with the SPSS package version 11.0 (Statistical Product and Service Solutions 11.0; SPSS Inc, Chicago, Ill).

Results

- The ANOVA-test revealed no significant group effect of the diagnosis for the volume of the right and left MD.
- There was no significant difference in the volume of the left and right MD between the patients with an unipolar and patients with a bipolar disease.
- There were no significant correlations between the length of illness and the volume of the right and left MD.
- There were no significant effects of diagnosis or interaction involving the diagnosis for the asymmetry coefficient.
- The volume of the right MD ($p=0,020$) and left ($p=0,012$) MD was significantly larger in patients who committed suicide, compared to patients with other causes of death.**

Discussion

- The present results suggest that the volume of the MD is not altered in patients with an affective disease.
- This result is consistent with the results of the study by Young et al (2004). In this neuropathological study no significant difference was found in the volume of the MD between patients with an unipolar disease, bipolar disease and normal controls.
- However, the volume of the right MD ($p=0,020$) and left ($p=0,012$) MD was significantly larger in affective patients who committed suicide, compared to affective patients with other causes of death. This result is consistent with a previous neuropathological study that reported significant structural differences in the brain stem of patients who committed suicide in comparisons (Bielau et al 2005).
- In conclusion, the present results suggest that patients with an affective disease who committed suicide may have distinct neuropathological characteristics.

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