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Volume and neuron number of the mediodorsal thalamic nucleus in schizophrenia: A replication study

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Abstract

Previous neuropathological studies on the mediodorsal thalamic nucleus (MD) in schizophrenia have yielded conflicting results. While some studies suggested that patients with schizophrenia have a pronounced reduction of the volume and neuron number in the MD, more recent data have not found anatomical alterations in this thalamic nucleus. However, most studies have considerable methodological shortcomings. In the present study, we investigated the volume, neuron density and neuron number in the left and right MD in patients with schizophrenia ($n=20$) and normal control subjects without neuropsychiatric disorders ($n=18$). Patients with schizophrenia showed no significant difference in neuron density and total neuron number in the MD. Compared with the control group, patients with schizophrenia had a smaller MD volume in both hemispheres, a difference that approached significance in the left MD (−7.3%) when the whole brain volume was included as a covariate. No significant main group effect of diagnosis was found for the right MD volume. There were no significant correlations between MD volume, neuron density, total neuron number and the duration of illness or the age of the patients. Taken together, the present results suggest that schizophrenia is associated with a moderate volume reduction in the left mediodorsal thalamic nucleus, while the neuron density and the total neuron number are unchanged.

Keywords: Psychosis; Thalamus; Neuropathology; Postmortem

1. Introduction

The mediodorsal thalamic nucleus (MD) is regarded as an association nucleus (Dekaban, 1953) due to its connections with different association cortical regions, such as the dorsolateral prefrontal cortex and the inferior parietal cortex (Goldman-Rakic

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and Porrino, 1985; Schmahmann and Pandya, 1990; Siwek and Pandya, 1991). According to a hypothesis by Guillery (1995), the MD is likely to play a key role in the communication between cortical association areas. According to the disconnection hypothesis of schizophrenia (Friston and Frith, 1995), the clinical phenomena are best understood as abnormal interactions between dorsolateral prefrontal cortex and temporal lobe areas, such as the superior temporal gyrus. Both these areas are regarded as heteromodal association areas (Pearlson et al., 1996). Therefore, it appears plausible that MD pathology may lead to disturbed interaction between these cortical association areas.

There is also evidence from postmortem (Pakkenberg, 1990, 1992; Popken et al., 2000; Young et al., 2000; Byne et al., 2002) and magnetic resonance imaging studies (Byne et al., 2001; Kemether et al., 2003; Hazlett et al., 2004) for anatomical abnormalities in the MD in schizophrenia. A recent study also showed a schizophrenia-associated reduced expression of homeobox genes in the MD (Kromkamp et al., 2003).

Some of these postmortem studies reported pronounced reductions in the cell number and the volume of the mediodorsal nucleus (Pakkenberg, 1990, 1992; Popken et al., 2000; Young et al., 2000; Byne et al., 2002). However, other postmortem studies have not found significant volume or neuron number reductions in the MD (Rosenthal and Bigelow, 1972; Lesch and Bogerts, 1984; Falke et al., 2000; Cullen et al., 2003; Dorph-Petersen et al., 2004).

The results of these postmortem studies are limited by relevant methodological shortcomings. The majority of studies have not reported the precise anatomical criteria for the delineation of the MD, have investigated only one brain hemisphere (Rosenthal and Bigelow, 1972; Lesch and Bogerts, 1984; Popken et al., 2000; Young et al., 2000; Byne et al., 2002; Dorph-Petersen et al., 2004), or have summed up the MD volumes in both hemispheres (Pakkenberg, 1990, 1992). Other studies had small sample sizes for the patient and control groups (Popken et al., 2000; Young et al., 2000).

In a previous study, our group reported a volume reduction of the left MD in schizophrenia patients (Danos et al., 2003). The present study is an extension of this work with an enlarged sample, and with the addition of assessments of neuron density and neuron number in the left and right sides of the MD.

2. Methods

2.1. Subjects

Postmortem brain tissue of 20 patients with schizophrenia (10 males, 10 females) and 18 matched normal control subjects (10 males, 8 females) were used for the present study (Table 1). All brains were obtained from the new Magdeburg brain collection. Patients and normal controls died between the years 1986 and 1993. Age ranged from 33 to 66 years. Demographic details are summarized in Table 1. Only patients with well-preserved and extensive clinical records were selected for this study. All patients were diagnosed according to DSM-IV (American Psychiatric Association, 1994) criteria. All subjects with schizophrenia had histories of inpatient hospitalization.

The mean duration of illness was 21.4 ± 9.8 (mean $\pm$ S.D.) years. The following DSM-IV subtypes of schizophrenia were defined according to the most significant and predominant characteristics: 12 had predominant paranoid symptoms (DSM-IV subtype 295.3), three had predominant mixed symptoms (DSM-IV subtype 295.9), three had a residual type (DSM-IV subtype 295.6), and two had predominant catatonic symptoms (DSM-IV subtype 295.2).

Table 1
Demographic details of the patients with schizophrenia and normal control subjects

	Control	Schizophrenia	*P*
Number	18	20	
Sex (M/F)	10/8	10/10	0.73[a]
Age (years)	52.6 (9.9)	52.9 (8.7)	0.87[b]
Duration of illness (years)	–	21.4 (9.8)	–
Postmortem interval (h)	34.1 (18.5)	43.5 (18.3)	0.12[c]
Fixation interval (months)	8.7 (7.3)	7.3 (2.7)	0.46[b]
Whole brain volume (mm^3)[d]	1251 (153)	1274 (134)	0.64[b]

Values are mean with S.D. in parentheses.
[a] Fischer's exact test.
[b] Student's *t*-test.
[c] Mann–Whitney test.
[d] Fresh weight of the brain. Data for four patients missing.

All patients had received a cumulative dose of classical neuroleptics. Due to the long duration of illness, the precise cumulative neuroleptic exposure could not be estimated. However, it is known that the duration of illness is correlated with the cumulative neuroleptic exposure (Nopoulos et al., 2001).

One potential confounding variable in the present study is the lack of information about neuroleptic medication during the terminal period of the subjects.

Brains with lifetime 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. Additionally, quantitative neuropathological changes due to neurodegenerative disorders (e.g., Alzheimer's, Parkinson's or Pick's disease), tumors, and inflammatory, vascular, or traumatic processes were ruled out by an experienced neuropathologist. Control brains without a history of neuropsychiatric disorders were obtained from the same pathological institutes or medical examiner's officers. Medical records from control subjects were reviewed to determine whether they had an active psychiatric disorder at the time of death and/or earlier in their lives. Brain volumes were calculated by the weight method (Yamada et al., 1999) using the fresh whole brain weight and the brain density.

No significant differences were found in the age, fixation interval (Student's *t*-test), whole brain volume, and gender distribution (Fisher's exact test) between the schizophrenia group and the control group. There was a trend towards a significant difference (0.12) in the postmortem interval between the two groups (Mann–Whitney test).

A stepwise multiple regression analysis was performed to control for the possible influence of whole brain volume, age, postmortem interval, fixation on the volume, neuron density and total neuron number of the left and right MD (Cotter et al., 2001). The *P* value threshold for inclusion of a new variable was chosen to be $P<0.008$ (0.05/6, after Bonferroni correction). The partial correlation factors for each of the variables, like the multiple correlation factor itself, were without significance.

2.2. Tissue processing

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 μm and mounted. Every 50th section was stained according to the combined Nissl (cresyl echt violet) and myelin (Heidenhain–Wölcke) procedure (Zech et al., 1986). Thus, 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.

The thickness of each section was determined with a 100× oil immersion objective, since it is known that section thickness is decreased after histological processing. The thickness of the section was determined by focusing the upper and lower surfaces of the section, and then subtracting the *z*-axis coordinate of the lower surface from that of the upper surface. The movements in the *z*-axis were measured with a microcator as an integral part of the Leica DM RB microscope (Leica, Gießen, F.R.G.). The section thickness after the histological procedures was 18.7 ± 1.1 μm (mean ± S.D.).

2.3. Morphometric analysis

Morphometric analysis was performed by a single observer (A.S.) 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, 2.5× objective) (Fig. 1). The volume of the whole MD including all subnuclei (parvocellular, densocellular, magnocellular) was assessed in the present study. The 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 pulvinar 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

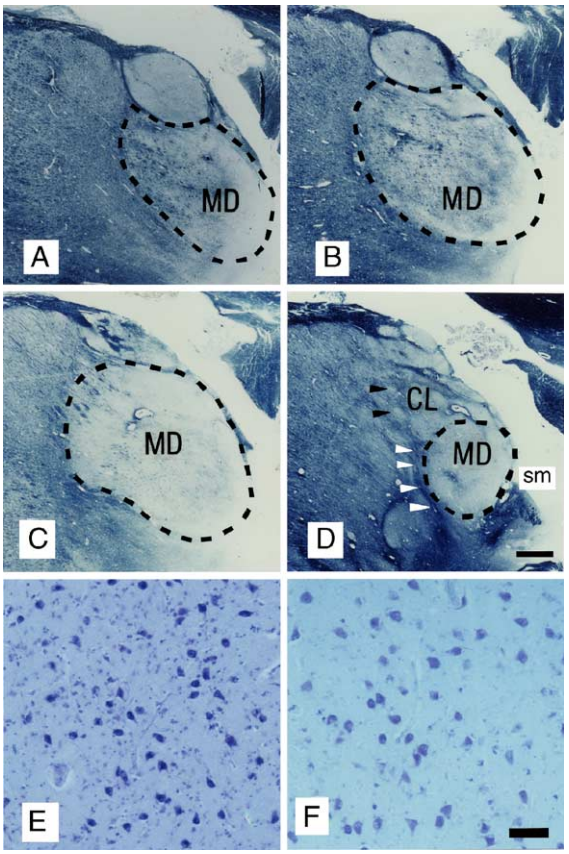

Fig. 1. (A–D) A sequence of low-power photomicrographs of coronal sections through the thalamus, stained with a combined Nissl-myelin staining in antero-posterior order. Levels B and C are 1 and 2 mm posterior to Level A. Level D is at the level approximately 9 mm posterior to Level A. The dashed line delineates the boundaries of the mediodorsal nucleus (MD). (D) Photomicrograph of a section located at the level of the stria medullaris (sm). White arrowheads indicate the lateral part of the internal medullary lamina, as it surrounds the lateral surface of the mediodorsal nucleus. Black arrowheads point to the islands of cells embedded within the central lateral nucleus (CL) (Hirai and Jones, 1989). (E and F) Nissl-stained neurons in the MD of a control subject (E) and in a patient with schizophrenia (F). Scale bars, (A–D) 1 mm; (E and F) 50 μm.

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 perimeters of the analysed nuclei were delineated on each section in which they were present. Volumes were calculated from areas measured in the performance of morphometrical operations previously described in detail (Bogerts et al., 1990).

The observed coefficients of error (OCE) for the individual estimates of volume and neuron density were calculated for 20 cases as described by Gundersen and Jensen (1987). For the measures of volume, the mean OCE values were as follows: 0.04 for the right MD, 0.03 for the left MD. For the neuron density, the mean OCE values were 0.04 for the right MD and 0.03 for the left MD. These data indicate that the measures are of adequate reliability and accuracy.

To establish interrater reliability (intraclass correlation) for the investigated volumes, repeated measurements for nine randomly selected brains were carried out by two tracers (A.S., R.S.). The intraclass correlations for the volumes were calculated for absolute size in millimeters. The intraclass correlation coefficients (Shrout and Fleiss, 1979) were 0.87 for the right MD and 0.83 for the left MD.

The number of neuronal profiles were measured separately in the MD of the right and left hemispheres of schizophrenic patients and controls. For the measurement of the neuronal profiles, we used a two-dimensional counting frame. The advantages and limitations of cell counting with a two-dimensional counting frame (Benes and Lange, 2001) and a three-dimensional counting frame (Gundersen et al., 1999) have already been described in detail. The main advantage of the three-dimensional paradigm compared with the two-dimensional method is the higher level of unbiasedness, especially for thick frozen sections (Heinsen et al., 2000). However, in the present study, we chose the two-dimensional cell counting method because we used thin paraffin-embedded sections with a thickness of 18.7 μm after the histological procedures. For such sections, a two-dimensional cell-counting paradigm includes all of the neuronal profiles present along the entire z-axis of the section. Therefore, the confounding effect of tissue collapse in this plane is substantially reduced (Benes and Lange, 2001).

The Leica DM RB microscope (Leica, Giessen, F.R.G., magnification 40×) was connected to a video camera (Kappatechnik, Gleichen, F.R.G.), and the

image was displayed on a computer monitor. The two-dimensional counting frame was then superimposed on the image using the Digitrace software (Imatec, Neufahrn, F.R.G). The dimension of the counting frame were 100×100 μm. The counting frame were superimposed on three sections along the rostral-caudal extent of the right and left MD. The sections were defined at 16 mm, 16.5 mm and 17 mm caudal to the anterior commissure. All profiles whose nucleoli were either completely within the counting frame or intersecting the right or bottom of the box were counted using a software system (Imatec, Neufahrn, F.R.G.) Neuronal profiles were only counted if they contained a clearly visible nucleolus. Neuron densities were estimated by correcting the number of profiles according to Abercrombie's (1946) correction formula and section thickness, and the estimated numerical density per cubic millimeter was determined. For each case, data from the counting areas were summed. The mean ($\pm$S.D.) number of neurons sampled per case was 128.9 ($\pm$21.4).

The intraclass correlation coefficients (Shrout and Fleiss, 1979) for the neuron-counting procedures were 0.86 for the right MD and 0.81 for the left MD. The total number of neurons in the MD was estimated by multiplying the average counting frame neuronal density and the calculated volume of MD.

2.4. 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, postmortem 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.

Because of the nonnormal distribution of the postmortem interval, the nonparametric Mann–Whitney test was used to determine differences between the schizophrenia group and the control group.

For the statistical analyses, analyses of variance (ANOVA) was chosen because of multiple determinations within each subject (Siegel et al., 1993).

MD volume, neuron density or total neuron number were analyzed by three-way ANOVAs with diagnosis and gender as grouping factors and hemisphere (left/right) as the repeated measure. Separate two-way 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 and the total neuron number with the whole brain volume as a covariate. Since there was a trend (0.12) towards a difference in postmortem interval (Table 1), we have also calculated three-way ANOVAs for each hemisphere with postmortem interval and brain volumes as covariates. If a group effect was observed for diagnosis, then follow-up *t*-tests were performed. Since this is a replication study, statistical significance was set for the *t*-tests at $P<0.05$, one-tailed.

Due to the sample size, statistical evaluation of the differences within the schizophrenia group ($n=20$) in the MD data (volume, neuron density and total neuron number of left and right MD) between the DSM-IV subtypes was performed between the paranoid subtype ($n=12$) and the other subtypes (residual, undifferentiated, catatonic) ($n=8$). For this purpose, two-way ANOVAs were performed with diagnosis as grouping factor and hemisphere as repeated measure.

For the analysis of possible lateralization effects, asymmetry coefficients were calculated for the volume, neuron density and total neuron number $[(\delta)=(\text{Right}-\text{Left})/(\text{Right}+\text{Left})\times 100)]$ according to Highley et al. (1999). Two-way ANOVAs were used for the asymmetry coefficients with gender and diagnosis as grouping factors.

For the ANOVAs, statistical significance was defined at $P<0.05$. Pearson's correlation coefficients were performed to examine the associations between age, length of illness and MD volume, neuron density and total neuron number in the left and right MD, and between whole brain volume and volume of the right and left MD. For the Pearson's correlation coefficients and for the stepwise multiple regression analysis, statistical significance was set at $P<0.006$ with Bonferroni correction (0.05/8).

Statistical analyses were performed with SPSS package version 11.0 (Statistical Product and Service Solutions 11.0; SPSS Inc, Chicago, IL, USA).

3. Results

The main results are summarized in Table 2. The three-way ANOVA for neuron density ($F_{1,38}=0.12$, $P=0.73$) or total neuron number ($F_{1,38}=1.06$, $P=0.30$) showed no significant main group effect of diagnosis. Inclusion of the whole brain volume as a covariate provided very similar results. The three-way ANOVA for MD volume revealed no significant main group effect of diagnosis ($F_{1,38}=2.16$, $P=0.15$) before adjustment for whole brain volume.

In the separate two-way ANOVAs for each hemisphere with whole brain volume as a covariate, there was a difference (−7.3%) in the left MD volume that approached significance ($F_{1,34}=3.65$, $P=0.06$), such that patients had a smaller volume. In addition, we have calculated three-way ANOVAs for each hemisphere with postmortem interval and brain volumes as covariates. A follow-up one-tailed *t*-test for the left MD volume revealed a trend ($P=0.11$) towards a volume reduction in the schizophrenia group. The effect of diagnosis on the left MD volume in the ANOVA became nonsignificant ($F_{1,34}=2.12$, $P=0.15$) after covarying with the whole brain volume and the postmortem interval.

Table 2
The neuron density, total neuron number and volume in the right and left MD in patients with schizophrenia ($n=20$) and normal control subjects ($n=18$)

	Control	Schizophrenia	
	Mean (S.D.)	Mean (S.D.)	Difference (%)
MD volume (mm^3)			
Left[a]	950 (113)	880 (175)	−7.3
Right	962 (115)	901 (184)	−6.3
MD neuron density ($/mm^3$)			
Left	6335 (1388)	6429 (787)	+1.4
Right	6541 (1201)	6759 (995)	+3.3
MD total neuron number (10^6)			
Left	6.05 (1.71)	5.58 (0.96)	−7.7
Right	6.39 (1.44)	6.01 (1.15)	−5.9

[a] ANOVA: Diagnosis, $F_{1,34}=3.65$, $P=0.06$, with the whole brain volume as a covariate; Diagnosis, $F_{1,34}=1.62$, $P=0.21$, with the whole brain volume and the postmortem interval as covariates. Follow-up one-tailed *t*-test: $P=0.11$.

No significant main group effect of diagnosis was found for the right MD volume in the ANOVAs. No significant diagnosis × hemisphere interactions and no significant diagnosis × gender interactions were found in the ANOVAs.

Within the schizophrenia group, the two-way ANOVA with diagnosis as grouping factor and hemisphere as repeated factor revealed no significant difference in the volume ($F_{1,20}=0.08$, $P=0.77$), neuron density ($F_{1,20}=0.01$, $P=0.92$) and total neuron number ($F_{1,20}=0.03$, $P=0.85$) between the paranoid subtype ($n=12$) and the other subtypes ($n=8$).

No significant correlations were found between either the age of the patients or the duration of disease and the MD volume, neuron density or total neuron number. There were no significant effects of diagnosis or interaction involving the diagnosis for the asymmetry coefficient (δ).

4. Discussion

In summary, the current study found no effect of diagnosis on the neuron density and total neuron number in the MD in schizophrenia. There was a difference in the left MD volume that approached significance when the whole brain volume was included as a covariate, such that patients had a smaller volume. However, this difference became nonsignificant after covarying with the whole brain volume and the postmortem interval. The result of the inclusion of the postmortem interval as a covariate in the ANOVAs might be regarded as problematic, since the correlations between the postmortem interval and the right and left MD volume were not significant. However, there was a trend (0.12) towards a significant difference in the postmortem interval between the two groups. In previous postmortem studies on the MD in schizophrenia, there is no consensus regarding the inclusion of the postmortem interval as a covariate in the statistical analysis. In the study by Falke et al. (2000), the postmortem interval was not significantly correlated with the postmortem interval and it was not included in the statistical analysis. However, in the studies by Dorph-Petersen et al. (2004) and Young et al. (2000), the postmortem interval was included as a covariate in the statistical

analysis, although the postmortem interval was not significantly different between the schizophrenia group and the normal control group. Therefore, it is still unclear whether the inclusion of the postmortem interval in the statistical analysis of the present study improves the validity of the results.

This result of a schizophrenia-associated left-sided MD volume reduction is consistent with our previous study with a smaller sample size, that reported a significant MD volume reduction only in the left hemisphere (Danos et al., 2003) and with a structural MRI study by Byne et al. (2001). This study (Byne et al., 2001) reported a significant MD volume reduction in schizophrenia only in the left hemisphere.

In the present study, there was no significant difference in the asymmetry coefficients in the MD volume, neuron density and total neuron number between the schizophrenia group and the control group. The lack of significance of the asymmetry coefficient for the MD volume is due to the non-significant volume reduction in the right MD. The only postmortem study that has investigated the MD in both hemispheres separately (Cullen et al., 2003) reported no evidence of asymmetry in the MD volume or neuron number. In a recent study (Highley et al., 2003), a significant volume reduction in the right medial and lateral pulvinar was found in schizophrenia. However, no asymmetry coefficients were reported in this study.

The schizophrenia-associated volume reduction in the left MD in our study (−7.3%) is very similar to the significant percentage reduction in the MD volume (−6.7%) in schizophrenia, reported by a recent structural MRI study (Kemether et al., 2003). The present results are partly consistent with previous postmortem studies (Rosenthal and Bigelow, 1972; Lesch and Bogerts, 1984; Falke et al., 2000; Cullen et al., 2003; Dorph-Petersen et al., 2004) that did not find significant reductions of volume and total neuron number in the MD in schizophrenia.

Several postmortem studies (Pakkenberg, 1990, 1992; Young et al., 2000; Popken et al., 2000; Byne et al., 2002) reported pronounced reductions of volume and neuron number in the MD in schizophrenia. However, all of these studies have several methodological shortcomings, especially in the estimation of MD volume.

In these studies (Pakkenberg, 1990, 1992; Popken et al., 2000; Young et al., 2000; Byne et al., 2002), the MD has been delineated according to different anatomical criteria (Eidelberg and Galaburda, 1982; Hirai and Jones, 1989; Ray and Price, 1993; Jones, 1997). The magnitude of the differences across studies in the estimation of the MD volume was quite large (Dorph-Petersen et al., 2004).

In the majority of studies that reported a reduction of the volume and the total neuron number in the MD, neuron density was not reduced (Popken et al., 2000; Young et al., 2000; Byne et al., 2002). In the study by Pakkenberg (1990), the neuron density was not reported. Therefore, it appears plausible that the inconclusive results regarding the total neuron number in the MD are mainly due to differences in the estimation of the MD volume.

Furthermore, the sample sizes of patients and normal controls investigated in the studies with pronounced volume and neuron number reductions were relatively small. Another methodological limitation is that almost all postmortem studies have analyzed only one hemisphere (Rosenthal and Bigelow, 1972; Lesch and Bogerts, 1984; Popken et al., 2000; Young et al., 2000; Byne et al., 2002; Dorph-Petersen et al., 2004), have analyzed the summation of both hemispheres (Pakkenberg, 1990, 1992), or have not differentiated between the hemispheres (Falke et al., 2000).

The two most recent postmortem studies on the MD in schizophrenia (Cullen et al., 2003; Dorph-Petersen et al., 2004) have not detected significant schizophrenia-associated reductions in the volume or total neuron number in the MD. In both studies, the delineation of the MD was precisely described. However, in the study by Dorph-Petersen et al. (2004), only the left hemisphere was investigated, the sample of controls being relatively small. A methodological limitation of the study by Cullen et al. (2003) is that the subjects with schizophrenia and control subjects were relatively old, with a mean age of 68 and 71, respectively.

In the present study, within the schizophrenia group, there was no significant difference in the MD volume, neuron density and total neuron number between the paranoid subtype ($n=12$) and the other subtypes. To our knowledge, this issue has not been addressed in the previous postmortem studies on the

MD (Rosenthal and Bigelow, 1972; Lesch and Bogerts, 1984; Pakkenberg, 1990; Falke et al., 2000; Popken et al., 2000; Young et al., 2000; Byne et al., 2002; Dorph-Petersen et al., 2004) or other thalamic nuclei in schizophrenia (Danos et al., 1998; Young et al., 2000; Danos et al., 2002).

It appears unlikely that the present finding of a volume reduction in the left MD in the schizophrenia group is due to the influence of neuroleptic medication in these patients, since previous studies suggest that thalamic volumes may be increased by neuroleptic medication (Gur et al., 1998). Additionally, a recent experimental study in monkeys has found no evidence for a relevant effect of neuroleptic medication on the volume and neuron number in the MD (Dorph-Petersen et al., 2004). Furthermore, if the thalamic reductions were due to neuroleptic treatment, one might have expected a negative correlation between the duration of illness and the volumes of the implicated thalamic nuclei, since the duration of neuroleptic treatment corresponds approximately to the duration of illness. However, in our study, no significant correlations were found between the length of illness and the volume, neuron density or total neuron number in the MD.

Taken together, the present results suggest that schizophrenia is associated with a moderate volume reduction in the left MD while the neuron density and the total neuron number are unchanged.

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References

Abercrombie, M., 1946. Estimation of nuclear population from microtome sections. Anatomical Record 94, 239–247.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Press, Washington, DC.

Benes, F.M., Lange, N., 2001. Two-dimensional versus three-dimensional cell counting: a practical perspective. Trends in Neuroscience 24, 11–17.

Bogerts, B., Falkai, P., Haupts, M., Greve, B., Ernst, St., Tapernon-Franz, U., Heinzmann, U., 1990. Post-mortem volume measurements of limbic system and basal ganglia structures in chronic schizophrenics. Schizophrenia Research 3, 295–301.

Byne, W., Buchsbaum, M.S., Kemether, E., Hazlett, E.A., Shinwari, A., Mitropoulou, V., Siever, L.J., 2001. Magnetic resonance imaging of the thalamic mediodorsal nucleus and pulvinar in schizophrenia and schizotypal personality disorder. Archives of General Psychiatry 58, 133–140.

Byne, W., Buchsbaum, M.S., Mattiace, L.A., Hazlett, E.A., Kemether, E., Elhakem, S.L., Purohit, D.P., Haroutunian, V., Jones, L., 2002. Postmortem assessment of thalamic nuclear volumes in subjects with schizophrenia. American Journal of Psychiatry 159, 59–65.

Cotter, D., Mackay, D., Landau, S., Kerwin, R., Everall, I., 2001. Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. Archives of General Psychiatry 58, 545–553.

Cullen, T.J., Walker, M.A., Parkinson, N., Craven, R., Crow, T.J., Esiri, M.M., Harrison, P.J., 2003. A postmortem study of the mediodorsal nucleus of the thalamus in schizophrenia. Schizophrenia Research 60, 157–166.

Danos, P., Baumann, B., Bernstein, H.G., Franz, M., Stauch, R., Northoff, G., Krell, D., Falkai, P., Bogerts, B., 1998. Schizophrenia and anteroventral thalamic nucleus: selective decrease of parvalbumin-immunoreactive thalamocortical projection neurons. Psychiatry Research 82, 1–10.

Danos, P., Baumann, B., Bernstein, H.G., Stauch, R., Krell, D., Falkai, P., Bogerts, B., 2002. The ventral lateral posterior nucleus of the thalamus in schizophrenia: a post-mortem study. Psychiatry Research 114, 1–9.

Danos, P., Baumann, B., Kramer, A., Bernstein, H.G., Stauch, R., Falkai, D., Bogerts, P., 2003. Volumes of association thalamic nuclei in schizophrenia: a postmortem study. Schizophrenia Research 60, 141–155.

Dekaban, A., 1953. Human thalamus. An anatomical, developmental and pathological study. Journal of Comparative Neurology 99, 639–667.

Dorph-Petersen, K.A., Pierri, J.N., Sun, Z., Sampson, A.R., Lewis, D.A., 2004. Stereological analysis of the mediodorsal thalamic nucleus in schizophrenia: volume, neuron number, and cell types. Journal of Comparative Neurology 472, 449–462.

Eidelberg, D., Galaburda, A.M., 1982. Symmetry and asymmetry in the human posterior thalamus: I. Cytoarchitectonic analysis in normal persons. Archives of Neurology 39, 325–332.

Falke, E., Han, L.Y., Arnold, S.E., 2000. Absence of neurodegeneration in the thalamus and caudate of elderly patients with schizophrenia. Psychiatry Research 93, 103–110.

Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? Clinical Neuroscience (New York) 3, 89–97.

Goldman-Rakic, P.S., Porrino, L.J., 1985. The primate mediodorsal (MD) nucleus and its projection to the frontal lobe. Journal of Comparative Neurology 242, 535–560.

Guillery, R.W., 1995. Anatomical evidence concerning the role of the thalamus in corticocortical communication: a brief review. Journal of Anatomy 187, 583–592.

Gundersen, H.J., Jensen, E.B., 1987. The efficiency of systematic sampling in stereology and its prediction. Journal of Microscopy 147, 229–263.

Gundersen, H.J., Jensen, E.B., Kieu, K., Nielsen, J., 1999. The efficiency of systematic sampling in stereology-reconsidered. Journal de Microscopie 193, 199–211.

Gur, R.E., Maany, V., Mozley, D., Swanson, C., Bilker, W., Gur, R.C., 1998. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. American Journal of Psychiatry 155, 1711–1717.

Hazlett, E.A., Buchsbaum, M.S., Kemether, E., Bloom, R., Platholi, J., Brickman, A.M., Shihabuddin, L., Tang, C., Byne, W., 2004. Abnormal glucose metabolism in the mediodorsal nucleus of the thalamus in schizophrenia. American Journal of Psychiatry 161, 305–314.

Heinsen, H., Arzberger, T., Schmitz, C., 2000. Celloidin mounting (embedding without infiltration)—a new, simple and reliable method for producing serial sections of high thickness through complete human brains and its application to stereological and immunohistochemical investigations. Journal of Chemical Neuroanatomy 20, 49–59.

Highley, J.R., McDonald, B., Walker, M.A., Esiri, M.M., Crow, T.J., 1999. Schizophrenia and temporal lobe asymmetry. A postmortem stereological study of tissue volume. British Journal of Psychiatry 175, 127–134.

Highley, J.R., Walker, M.A., Crow, T.J., Esiri, M.M., Harrison, P.J., 2003. Low medial and lateral right pulvinar volumes in schizophrenia: a postmortem study. American Journal of Psychiatry 160, 1177–1179.

Hirai, T., Jones, E.G., 1989. A new parcellation of the human thalamus on the basis of histochemical staining. Brain Research Brain Research Reviews 14, 1–34.

Jones, E.G., 1997. A description of the human thalamus. In: Steriade, M., Jones, E.G., McCormick, D.A. (Eds.), Thalamus, Experimental and Clinical Aspects, vol. II. Elsevier, Amsterdam, pp. 425–487.

Kemether, E.M., Buchsbaum, M.S., Byne, W., Hazlett, E.A., Haznedar, M., Brickman, A.M., Platholi, J., Bloom, R., 2003. Magnetic resonance imaging of mediodorsal, pulvinar, and centromedian nuclei of the thalamus in patients with schizophrenia. Archives of General Psychiatry 60, 983–991.

Kromkamp, M., Uylings, H.B., Smidt, M.P., Hellemons, A.J., Burbach, J.P., Kahn, R.S., 2003. Decreased thalamic expression of the homeobox gene DLX1 in psychosis. Archives of General Psychiatry 60, 869–874.

Lesch, A., Bogerts, B., 1984. The diencephalon in schizophrenia: evidence for reduced thickness of the periventricular grey matter. European Archives of Psychiatry and Neurological Sciences 234, 212–219.

Nopoulos, P.C., Ceilley, J.W., Gailis, E.A., Andreasen, N.C., 2001. An MRI study of midbrain morphology in patients with schizophrenia: relationship to psychosis, neuroleptics, and cerebellar neural circuitry. Biological Psychiatry 49, 13–19.

Pakkenberg, B., 1990. Pronounced reduction of total neuron number in mediodorsal thalamic nucleus and nucleus accumbens in schizophrenics. Archives of General Psychiatry 47, 1023–1028.

Pakkenberg, B., 1992. The volume of the mediodorsal thalamic nucleus in treated and untreated schizophrenics. Schizophrenia Research 7, 95–100.

Pearlson, G.D., Petty, R.G., Ross, C.A., Tien, A.Y., 1996. Schizophrenia: a disease of heteromodal association cortex? Neuropsychopharmacology 14, 1–17.

Popken, G.J., Bunney, W.E., Potkin, S.G., Jones, E.G., 2000. Subnucleus-specific loss of neurons in medial thalamus of schizophrenics. Proceedings of the National Academy of Sciences of the United States of America 97, 9276–9280.

Ray, J., Price, J.L., 1993. The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in the macque monkeys. Journal of Comparative Neurology 337, 1–31.

Rosenthal, R., Bigelow, L.B., 1972. Quantitative brain measurements in chronic schizophrenia. British Journal of Psychiatry 121, 259–264.

Schmahmann, J.D., Pandya, D.N., 1990. Anatomical investigation of projections from thalamus to posterior parietal cortex in the rhesus monkey: a WGA-HRP and fluorescent tracer study. Journal of Comparative Neurology 295, 299–326.

Siegel Jr., B.V., Buchsbaum, M.S., Bunney Jr., W.E., Gottschalk, L.A., Haier, R.J., Lohr, J.B., Lottenberg, S., Najafi, A., Nuechterlein, K.H., Potkin, S.G., Wu, J., 1993. Cortical–striatal–thalamic circuits and brain glucose metabolic activity in 70 unmedicated male schizophrenic patients. American Journal of Psychiatry 150, 1325–1336.

Siwek, D.F., Pandya, D.N., 1991. Prefrontal projections to the mediodorsal nucleus of the thalamus in the rhesus monkey. Journal of Comparative Neurology 312, 509–524.

Shrout, P.E., Fleiss, J.L., 1979. Intraclass correlations: uses in assessing rater reliability. Psychological Bulletin 86, 420–428.

Yamada, Y., Esaki, Y., Mizutani, T., 1999. Intracranial cavity volume can be accurately estimated from the weights of intracranial contents: confirmation by the dental plaster casting method. Neuropathology and Applied Neurobiology 25, 341–344.

Young, K.A., Manaye, K.F., Liang, C., Hicks, P.B., German, D.C., 2000. Reduced numbers of mediodorsal and anterior thalamic neurons in schizophrenia. Biological Psychiatry 47, 944–953.

Zech, M., Roberts, G.W., Bogerts, B., Crow, T.J., Polak, J.M., 1986. Neuropeptides in the amygdala of controls, schizophrenics and patients suffering from Huntington's chorea: an immunohistochemical study. Acta Neuropathologica 71, 259–266.