Eur Arch Psychiatry Clin Neurosci (2011) 261:47–58
DOI 10.1007/s00406-010-0119-9

ORIGINAL PAPER

A morphometric analysis of the septal nuclei in schizophrenia and affective disorders: reduced neuronal density in the lateral septal nucleus in bipolar disorder

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Received: 23 October 2009 / Accepted: 11 June 2010 / Published online: 7 July 2010

Abstract The septal nuclei are assumed to play a significant role in the pathophysiology of schizophrenia and affective disorders. The aim of this study was to morphometrically characterize the septal nuclei in patients with schizophrenia, bipolar disorder, and major depressive disorder, when compared with healthy control subjects. We analyzed the septal nuclei by determining the density and size of the neurons in postmortem brains in 17 patients with schizophrenia, 8 patients with bipolar disorder, 7 patients with major depressive disorder, and 14 control subjects matched for age and gender. There was a significant reduction in the neuronal density, but not in the mean cross-sectional area, in the lateral septal nucleus ($P = 0.013$) in patients with bipolar disorder when compared with control subjects. There were no significant changes in the neuronal density of the septal nuclei of the medial and lateral cell groups in patients with schizophrenia and major depressive disorder when compared with control subjects. There was a significant negative correlation between neuronal density in the lateral septal nucleus and disease duration in patients with major depressive disorder ($P = 0.037$, $r = -0.9$). The histopathological abnormality of the decreased neuronal density in the lateral septal nucleus, which is an important limbic region involved in emotions, might be a neuropathological correlate of bipolar disorder.

Keywords Septal nuclei · Neuroleptics · Bipolar disorder · Major depressive disorder

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Introduction

The septal region of the brain consists of the septum pellucidum and the septum verum (area septalis), which contains most of the septal nuclei. The septal nuclei connect to the hippocampus, the hypothalamus, the dorsal raphe nuclei, and the habenula, and the septal region is involved in the control of processes related to learning and memory, emotion, autonomic regulation, and feeding behavior [1]. The lateral septum is known to be integrated into the reward system [2] and is affected during emotional responses [3]. Its neurons project into the nucleus accumbens, which has essential connections to the limbic system [4]. The nucleus accumbens is another important part of the reward system and is affected in drug addiction [5]. Volume changes and a reduced number of neurons in the

nucleus accumbens [6] have been reported in patients with schizophrenia. Septal lesions in rats produce dramatic effects such as aggressive and avoidance behavior, which are associated with altered activity levels [7]. Lesions of the medial septal region in rats enhance latent inhibition [8] and impair learning and exploratory behavior [9]. Different subdivisions of the human septal region have been described in the literature. Brockaus [10] and Horvath and Palkovits [11] divide the septal tissue into lateral and medial cell groups. In contrast, Andy and Stephan [12] split the septal tissue into four groups: (i) a dorsal group with the nucleus septalis dorsalis, (ii) a ventral group with the nucleus septalis lateralis, (iii) a medial group with the nucleus septalis medialis, and the nucleus of the diagonal band of Broca and (iv) a caudal group with the nuclei septalis fimbrialis and triangularis and the bed nucleus of anterior commissure and stria terminalis. According to Horvath and Palkovits [11], the septal nuclei can be divided into lateral and medial cell groups. The medial cell group comprises the medial, triangular septal nucleus and the vertical part of nucleus of the diagonal band of Broca. Within the medial nucleus, the following subdivisions are important: pars dorsalis, pars ventralis, pars fimbrialis, pars intermedia and pars posterior. The lateral cell group comprises the dorsal and lateral septal nuclei. The lateral septal nucleus is composed of the following subdivisions: pars anterior, pars dorsalis, and pars ventralis [11]. Large neurons are found in the diagonal band of Broca and in the medial septal nucleus [13]. Lesions or dysgenesis of the septal region in patients might have cognitive and/or emotional effects. Vascular and tumoral lesions within the septal tissue might result in neuropsychiatric disturbances similar to schizophrenia, a depressed mood or psychotic symptoms [14] and early damage of the cholinergic septohippocampal pathway is seen in Alzheimer's disease [15]. Swollen septal tissue neurons have been described in the brains of young patients with schizophrenia [16]. The neurological disease Kuru is characterized by an increased size of the septal nuclei [17]. There are reports of spike and slow-wave activity occurring focally in the septal region of patients with schizophrenia during psychotic episodes [18]. A feedback loop between the septal region, the hippocampus, the amygdala, and the cerebellum and its involvement in emotional disorders has been suggested [19]. Volumetric and cellular changes in the limbic and cortical regions, such as the hippocampus, the anterior cingulate cortex, and the prefrontal cortex, are implicated in the neuropathology of affective disorders and schizophrenia [20, 21]. Therefore, a quantitative neurohistological study of several subdivisions of the septal nuclei, which are an important, but not frequently investigated limbic midline structure, in schizophrenia and affective disorders could provide additional insights into the histopathology of these diseases. The present study aimed to characterize the septal nuclei in terms of neuronal density (cells/mm^3) and neuronal size (μm^2) in patients with schizophrenia, bipolar disorder, and major depressive disorder and in control subjects without neuropsychiatric diseases matched for age, sex, and other confounding variables.

Materials and methods

Subjects

All brains used in this study were from the Magdeburg Brain Collection. The brains were obtained from pathologists or medical examiner offices from 1987 to 2002 according to German law and the Declaration of Helsinki 1975 and after approval by the local ethical commission of the University of Magdeburg. The mean demographic data for all individual cases (all were Caucasian), including brain weight, postmortem delay and duration of the disease are given in Table 1. The brains were divided into four groups, which were carefully matched for gender, age, postmortem delay, brain volume (4-Groups-ANOVA: $p_{gender} = 0.47$; $p_{age} = 0.25$; $p_{brain\ volume} = 0.43$; $p_{postmortem\ delay} = 0.52$), onset of illness (U-Test, Wilcoxon-Mann–Whitney; $p_{schizophrenics\ vs.\ major\ depression} = 0.085$; $p_{schizophrenics\ vs.\ bipolar} = 0.17$; $p_{bipolar\ vs.\ major\ depression} = 1.00$), and duration of disease (U-Test, Wilcoxon-Mann–Whitney; $p_{schizophrenics\ vs.\ major\ depression} = 0.005$; $p_{schizophrenics\ vs.\ bipolar} = 0.16$; $p_{bipolar\ vs.\ major\ depression} = 0.019$). The postmortem brains of 14 subjects without any signs of neurological or psychiatric

Table 1 Demographic data of control subjects, patients with schizophrenia, patients with bipolar disorder, and patients with major depressive disorder

	Male/female/age (years)	Brain volume (cm^3)	Postmortem delay (h)	Duration of disease (years)	Age of onset of disease (years)
Control subjects, mean (±SD)	6/8; 50.9 ± 9.2	1,266.8 ± 132.6	34.4 ± 17.3		
Patients with schizophrenia, mean (±SD)	10/7, 52.4 ± 8.1	1,269.8 ± 135.3	41.2 ± 19.8	20.1 ± 11.5	32.2 ± 11.6
Patients with bipolar disorder, mean (±SD)	5/3; 50.8 ± 11.9	1,379.3 ± 144.5	32.9 ± 24.0	15.1 ± 7.7	35.7 ± 8.3
Patients with major depressive disorder, mean (±SD)	2/5; 42.6 ± 12.4	1,294.7 ± 135.9	34.0 ± 15.2	4.5 ± 4.4	39.4 ± 12.5

Mean ± standard deviation

symptoms were used as a control group. Postmortem brains from 17 patients with schizophrenia according to DSM-IV and ICD 10 criteria were included; most of these patients had received antipsychotic treatment for several years. Additionally, the brains of 15 patients with affective disorders according to DSM-IV and ICD-10 criteria were included: 8 patients were diagnosed with bipolar disorder (DSM IV-TR: 296.5; F 31.3) including manic and depressive episodes, and 7 patients suffered from major depressive disorder (DSM IV-TR: 296.5; *F* 31.5). The level of typical neuroleptic and antidepressive medication in the last 3 months before death was assessed from medical records. Information for clinical diagnosis was obtained by the careful study of clinical records and/or by structured interviews with either the physicians involved in the treatment or persons who lived with or had frequently contact with the subjects before death. The DSM-IV diagnosis of schizophrenia, bipolar disorder or major depressive disorder was established by two experienced psychiatrists (H.B. and J.S.) in a consensus meeting. The same procedure was followed to exclude psychiatric disorders in the control subjects. The criteria for exclusion of the groups were the following: (i) organic brain disease (ii) brain injury (iii) alcoholism or chronic substance abuse (iv) chronic somatic diseases affecting the central nervous system (e.g. cachexia, cancer, chronic liver disease, chronic kidney disease or long term corticosteroid treatment), and (v) age above 65 years in order to exclude changes related to the normal aging of the brain.

Tissue processing

Brains were removed within 4–72 h after death (see Table 1 for demographic data of control subjects and psychiatric patients) and fixed in toto in 8% phosphate-buffered formaldehyde for at least 2 months (pH = 7.0, T = 15–20°C). The frontal and occipital poles were separated by coronal cuts anterior to the genu and posterior to the splenium of the corpus callosum with a calibrated microtome**.** After embedding all parts of the brains in paraffin, serial whole brain coronal sections, without a midline cut of the middle block, were cut (20 μm) and mounted. The middle block comprised the fronto-temporal lobe extending over the whole length of the corpus callosum, including the cortical areas, the thalamus, and the hippocampus. The shrinkage of brain tissue during paraffin embedding was obtained for each brain by calculating the ratio of identical distances between opposite cortical gyri on the most rostral and most caudal sections of the middle block before and after embedding [22]. The shrinkage factor caused by fixation and embedding and the thickness of slices were calculated using the following formula: $VF = (A1/A2)^{3/2}$ (VF = volume shrinkage factor; A1 = cross-sectional area before processing of tissue; A2 = cross-sectional area after processing of tissue). The mean volume shrinkage factor for patients with schizophrenia, major depressive disorder, and bipolar disorder and for control subjects was 2.21. No significant differences in the shrinkage factors were found among the four groups. Every 50th section was Nissl and myelin stained (Heidenhain/Woelcke). The distance between the sections was 1 mm.

Stereological based analysis

For the present study, three systematically uniform coronal sections were randomly sampled from each brain. Each section was located at the same clearly defined anatomical landmarks in the anterior, middle, and posterior portions of the human septum (see Fig. 1). The distance between each of the chosen coronal sections was 4 mm. The cross-sectional areas of the septal nuclei within each section were determined by a computerized imaging system (Digitrace Imaging System, Germany). The septal tissue was outlined under a microscope at low magnification with a 2.5× objective according to the borders established by Horvath and Palkovits [11] and Mai et al. [23] (see Fig. 1). The anterior border of the septal tissue was the genu of the corpus callosum, the lateral border was the lateral ventricles, the upper border was the body of the corpus callosum, the lower border was the anterior commissure, the basal borders were the nucleus accumbens and the stria terminalis, and the dorsal border was the fornix. To determine inter-rater reliability, stereological measurements of eight randomly selected brains were performed by three of the authors (H.B., R.B., and R.S). The inter-rater reliability was 0.79 (Intraclass Correlation Coefficient) for the neuronal density of the septal nuclei and 0.82 (Intraclass Correlation Coefficient) for the neuronal size of the septal nuclei. To determine intra-rater reliability, stereological measurements of four randomly selected brains were performed by one of the authors (R.B.). The intra-rater reliability was 0.81 (Intraclass Correlation Coefficient) for the neuronal density of the septal nuclei. All measurements were performed blind to the diagnosis, with the investigators unaware of the diagnosis, age, or gender of each sample. Glial cells were distinguished from neurons on the basis of their smaller size, absence of stained cytoplasm and darker nucleus. The cross-sectional area of each section was scanned with a 2.5× objective using a video camera module attached to a Leica light microscope and Digitrace software providing a picture on a monitor (22.0 mm × 15.9 mm). A magnification of 400× was used for the cell counting. The counting frame was superimposed on three different systematically uniform, randomly sampled sections at clearly defined anatomical landmarks with twenty systematically uniform randomly chosen

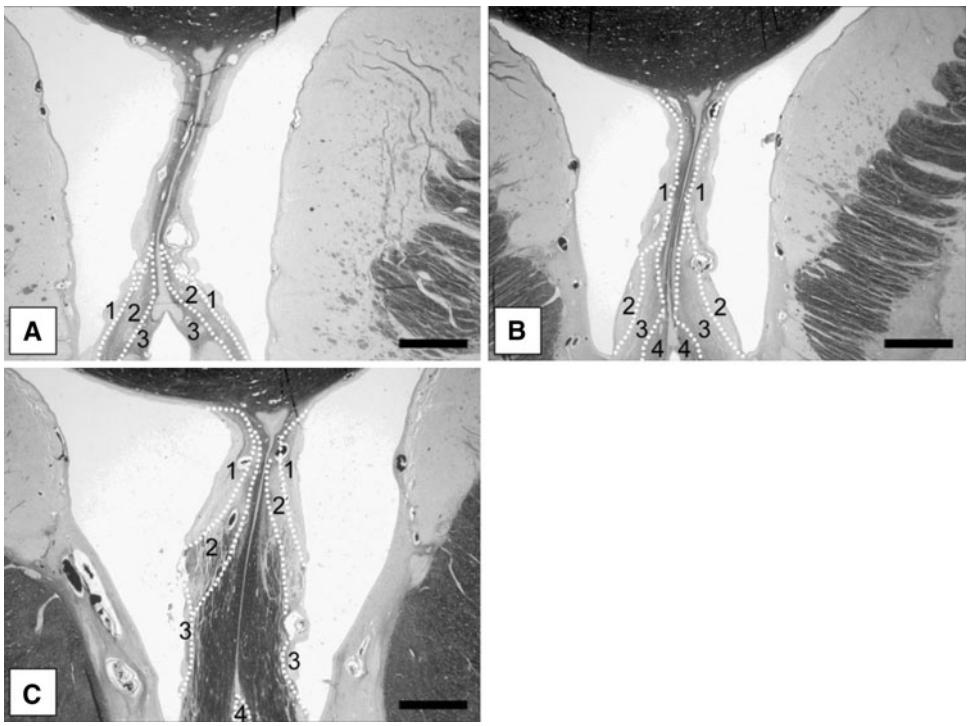

Fig. 1 Coronal sections of the human septum showing the septum in the anterior (**a**), middle (**b**), and posterior portion (**c**) at 2.5× magnification: **a** (*1*) Nucleus lateralis (pars anterior and pars ventralis) of the lateral cell group (*2*) Nucleus medialis (pars dorsalis and pars ventralis) of the medial cell group (*3*) Nucleus of the diagonal band of Broca (vertical part) of the medial cell group. Regions (*1–3*) were delineated according to the borders of Horvath and Palkovits (1987). **b** (*1*) Nucleus dorsalis of the lateral cell group (*2*) Nucleus lateralis (pars anterior and pars ventralis) of the lateral cell group (*3*): Nucleus medialis (pars dorsalis and pars ventralis) of the medial cell group (*4*) Nucleus of the diagonal band of Broca (vertical part) of the medial cell group. Regions (*1–4*) were delineated according to the borders of Horvath and Palkovits (1987). **c** (*1*) Nucleus dorsalis of the lateral cell group (*2*) Nucleus medialis (pars fimbrialis and pars intermedia) of the medial cell group. (*3*) Nucleus lateralis (pars ventralis and pars dorsalis) of the lateral cell group. Regions (*1–3*) were delineated according to the borders of Horvath and Palkovits (1987). 4 Nucleus triangularis of the medial cell group, which was delineated according to the borders of Mai et al. (1997). Scale bar corresponds in **a** to 3.4 mm and in **b** and **c** to 2.6 mm

counting boxes in the Ncl. medialis, the vertical part of the diagonal band of Broca, the Ncl. lateralis, and Ncl. dorsalis and with ten systematically uniform, randomly chosen counting boxes in the Ncl. triangularis along the entire extent of the septal nucleus using a video camera module attached to a Leica light microscope and Digitrace software. The actual thickness of each section was determined with a 100× oil immersion objective by focusing the upper and lower surfaces of the section and subtracting the *z*-axis coordinate of the lower surface from that of the upper surface. The movements of the *z*-axis were measured with a microcator as an integral part of the Leica DM RB microscope (Leica, Gießen, Germany). The actual section thickness measured at each dissector site was applied for the final calculation of the neuron number [24–26]. The average thickness of the sections (*z*-axis) was 16.1 µm ± 1.8 (mean ± SD). The mean thickness of the sections was 15.3 µm ± 1.7 (mean ± SD) among patients with schizophrenia, 16.8 µm ± 1.8 (mean ± SD) among patients with major depressive disorder, 17.3 µm ± 1.7 (mean ± SD) among patients with bipolar disorder, and 16.2 µm ± 1.5 (mean ± SD) among the control subjects. No significant differences in mean section thickness were found among the groups. Neurons touching the left and lower borders of the counting boxes were excluded and neurons touching the opposite borders were included (Fig. 2a and b). The dimensions of the optical dissector used were 139.4 µm × 139.4 µm (*x*, *y*) × 10 µm (*z*) for control subjects and patients with major depressive disorder, × 9 µm (*z*) for patients with schizophrenia, and × 11 µm (*z*) for patients with bipolar disorder, with a guard depth of 3 µm on top and bottom (see Fig. 2a and b). Only neurons with focused nucleoli within the dissector height were counted (see Fig. 2a and b). Because the number of neuronal profiles within the counting box (e.g., between the two planes of the dissector) and the square of the counting area (as determined by the square of the septal nuclei at the adjacent section) were identified, the number of neurons within a given tissue volume (neuronal density) could be calculated [26]. Neuronal sizes were measured by tracing around the perimeter of each neuron for all counted neurons with the cursor on the screen. All measurements

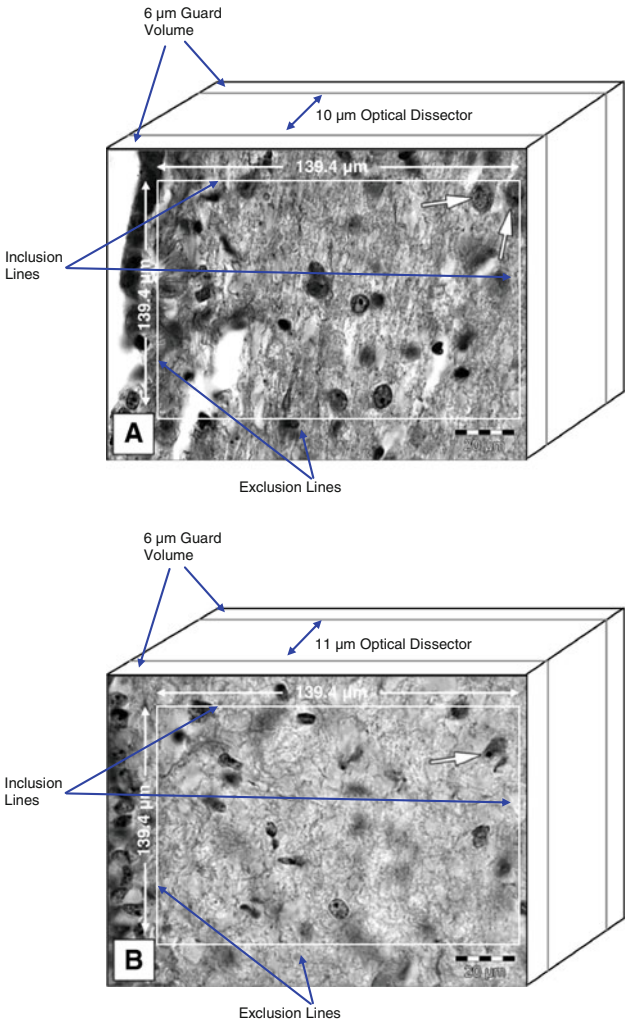

Fig. 2 Representative images of a combined Nissl (*for neurons*) and Heidenhain-Woelcke (*myelinated fiber*) staining of the septal nuclei at 100× magnification. **a** Nucleus lateralis (*pars ventralis*) of the lateral cell group of a control subject. **b** Nucleus lateralis (*pars ventralis*) of the lateral cell group of a patient with bipolar disorder. *Arrows* indicate neurons. Scale bar corresponds to 20 µm (modified after: Pennington K et al. (2008). Evidence for reduced neuronal somal size within the insular cortex in schizophrenia, but not in affective disorders. Schizophr Res 106: 164–171)

for neuronal sizes were obtained in $\mu m^2 \pm$ standard deviation. Neuronal sizes were estimated by automatically calculating (Digitrace Imaging System, Germany) the diameter of every traced neuronal profile as an equivalent circle. Neuronal sizes were corrected for tissue shrinkage.

Statistical analysis

The independence of frequency for the variables of gender and diagnosis was analyzed by Pearson's chi-squared test (chi-squared = 2.23; $df = 3$; $P = 0.528$). The other demographic variables were described as means ± SD and compared among the four groups using one-way ANOVA. Because some of the morphometric values had distinct asymmetric distributions, they were characterized by median and quartiles and analyzed by non-parametric tests. The Kruskal–Wallis test was performed to determine the significance of the differences in the mean cross-sectional area, neuron numbers, neuronal density, and neuron size among the four groups (e.g., control subjects, patients with bipolar disorder, patients with major depressive disorder, and patients with schizophrenia). The Kruskal–Wallis test had the null hypothesis that no significant differences exist among those four groups. The Kruskal–Wallis test did find significant differences among the four groups, but which group differed from the other groups could not be determined. Therefore, single tests with two groups were performed. Because the tests were carried out several times with the random samples (i. e., control subjects vs. patients with bipolar disorder, control subjects vs. patients with major depressive disorder, and control subjects vs. patients with schizophrenia), a Bonferroni-Holm correction was used. In cases of significance, the pairwise U-test (Wilcoxon-Mann–Whitney with Shaffer-correction) was used to detect significant differences between pairwise groups. Correlations were calculated using Spearman's correlation coefficient for the effects of duration of disease, mean dosage of antidepressants, neuroleptics, and lithium in the last 90 days preceding death.

Results

Neuronal density in the septal nuclei of patients with schizophrenia, bipolar disorder and major depressive disorder, and in control subjects

A significantly reduced neuronal density in the lateral septal nucleus (pars anterior, pars dorsalis, pars ventralis; $P = 0.013$, see Fig. 2a and b, Fig. 3; Table 2) was found in bipolar patients compared with control subjects, whereas

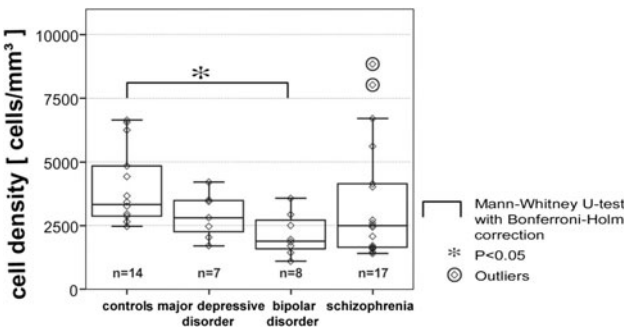

Fig. 3 Neuronal densities (cells/mm^3) of the lateral septal nucleus in patients with schizophrenia ($N = 17$), bipolar disorder ($N = 8$) and major depression ($N = 7$), and control subjects ($N = 14$). The box plots represent the median values

Table 2 Neuronal densities (cells/mm^3), neuronal sizes (μm^2) presented as median and quartiles (in parentheses) with standard deviation, and coefficient of error in septal nuclei of patients with schizophrenia (SZ), patients with bipolar disorder (BP), patients with major depressive disorder (MD), and control subjects (CTR)

Median (q_1; q_3)	Ncl. medialis/pars dorsalis and pars ventralis Medial cell group Cell density/cell size/ coefficient of error	Ncl. medialis/pars fimbrialis and pars intermedia Medial cell group Cell density/cell size/ coefficient of error	Ncl. triangularis Medial cell group Cell density/cell size/ coefficient of error	Diagonal band of Broca/vertical part Medial cell group Cell density/cell size/ coefficient of error	Ncl. lateralis/pars anterior, pars dorsalis and pars ventralis Lateral cell group Cell density/cell size/ coefficient of error	Ncl. dorsalis Lateral cell group Cell density/cell size/ coefficient of error
Control subjects $N = 14$	3,288 (2,792; 4,362)	2,404 (1,486; 3,467)	2,722 (1,979; 3,889)	2,447 (2,176; 3,002)	3,347 (2,880; 4,830)	1,416 (1,055; 2,641)
	65.4 (51.5; 80.9)	64.4 (54.1; 72.8)	45.2 (40.1; 55.3)	108.5 (69.4; 158.9)	55.5 (48.6; 60.7)	54.5 (46.3; 73.1)
	0.07	0.06	0.12	0.10	0.06	0.07
Patients with schizophrenia $N = 17$	2,448 (1,981; 3,426)	2,683 (1,310; 3,324)	1,909 (1,275; 6,501)	2,574 (1,302; 4,128)	2,516 (1,669; 4,150)	1,516 (994; 2,879)
	60.9 (49.1; 74.2)	57.6 (50.9; 74.7)	42.5 (39.2; 50.7)	83.1 (57.6; 134.9)	53.1 (46.1; 62.3)	53.9 (44.2; 67.3)
	0.07	0.08	0.16	0.09	0.06	0.07
Patients with bipolar disorder $N = 8$	2,119 (1,451; 3,221)	1,665 (1,207; 3,408)	462 (324; 2,858)	3,251 (1,714; 3,869)	1,905 (1,517; 2,834)	1,234 (620; 2,996)
	62.0 (49.2; 73.8)	74.0 (54.1; 85.1)	50.0 (37.2; 62.6)	125.1 (87.1; 197.8)	58.8 (44.6; 60.6)	49.6 (40.8; 66.8)
	0.08	0.09	0.17	0.12	0.07	0.09
Patients with major depressive disorder $N = 7$	2,757 (1,445; 3,661)	1,912 (1,863; 4,713)	2,498 (1,819; 5,401)	2,201 (1,737; 3,681)	2,817 (2,059; 3,529)	962 (788; 2,709)
	72.7 (57.9; 83.7)	78.1 (67.4; 84.6)	42.1 (38.5; 50.2)	144.9 (109.7; 213.7)	63.6 (53.0; 67.3)	56.7 (47.3; 62.4)
	0.06	0.06	0.11	0.07	0.04	0.06
KW-test (Ctr, MD, BP, SZ)	$P = 0.120$	$P = 0.810$	$P = 0.410$	$P = 0.880$	$P = 0.032$*	$P = 0.740$
MD vs. CTR[a]					$P = 0.520$	
BP vs. CTR[a]					$P = 0.013$*	
SZ vs. CTR[a]					$P = 0.420$	
BP vs. MD[a]					$P = 0.570$	
SZ vs. MD[a]					$P = 0.760$	
SZ vs. BP[a]					$P = 0.520$	

KW-test Kruskal–Wallis test

[a] Pairwise U-Tests (Schaffer-correction)

Table 3 Spearman correlation of neuronal density in the lateral septal nucleus vs. different parameters in patients with major depressive disorder and bipolar disorder

Septal nuclei versus	Cell density in the lateral					
	Patients with major depressive disorder			Patients with bipolar disorder		
	n	*r*	*P*-Value	*n*	*r*	*P*-Value
Duration of disease	5	−0.90	0.037*	8	−0.60	0.12
AD-90 days	7	−0.71	0.077	8	−0.11	0.86
NL-90 days	7	−0.61	0.14	8	0.66	0.076
BDZ-28 days	7	−0.41	0.36	8	−0.07	0.87
CBZ	7	–	–	8	−0.08	0.85
Sed-28 days	3	0.000	1.000	4	−0.11	0.89
Lithium	7	−0.41	0.36	8	0.37	0.37

AD mean dosage antidepressants in the last 90 days before death, *NL* typical Neuroleptics in the last 28 days before death, *BDZ* Benzodiazepine in the last 28 days before death, *CBZ* Carbamazepine, *Sed* Sedativa in the last 28 days before death

no significant differences were found in the other groups (bipolar patients vs. schizophrenic patients, $P = 0.52$; patients with major depressive disorder vs. bipolar patients, $P = 0.57$; patients with major depressive disorder vs. controls, $P = 0.52$; schizophrenic patients vs. controls, $P = 0.42$; schizophrenic patients vs. patients with major depressive disorder, $P = 0.76$). No significant differences in the neuronal density in the dorsal septal nucleus of the lateral cell group were found ($P = 0.74$) among patients with schizophrenia, bipolar disorder and major depressive disorder and the control subjects. No significant changes in neuronal density were observed in the medial cell group (pars dorsalis and pars ventralis, $P = 0.12$; pars fimbrialis and pars intermedia, $P = 0.81$; pars triangularis, $P = 0.41$; and the diagonal band of Broca, $P = 0.88$) among patients with schizophrenia, bipolar disorder and major depressive disorder and the control subjects (Table 2). The mean cross-sectional area of the septal nuclei also did not show significant differences among patients with schizophrenia, bipolar disorder and major depressive disorder and the control subjects. The predicted coefficient of error of the total number of cells in the Ncl. lateralis was 0.06 for the control subjects, 0.06 for patients with schizophrenia, 0.07 for patients with bipolar disorder, and 0.04 for patients with major depressive disorder (Table 2).

Neuronal sizes of the septal nuclei in patients with schizophrenia, bipolar disorder, and major depressive disorder

There were no significant differences in the neuronal sizes in the septal nuclei of the lateral cell groups (pars anterior, pars ventralis, and pars dorsalis of the lateral septal nucleus $P = 0.47$; dorsal septal nucleus $P = 0.83$) or in the medial cell group (pars dorsalis and pars ventralis, $P = 0.45$; pars fimbrialis and pars intermedia, $P = 0.22$; pars triangularis, $P = 0.81$; and the diagonal band of Broca, $P = 0.19$) among patients with schizophrenia, bipolar disorder and major depressive disorder and the control subjects. The neuronal sizes were corrected for shrinkage.

Correlation between increased neuronal density in the lateral septal nucleus and neuroleptic medication in patients with bipolar disorder

There was a trend toward a significant positive correlation between neuronal density in the lateral septal nucleus and typical neuroleptic dosage (for 90 days) in patients with bipolar disorder ($P = 0.076$, $r = 0.66$; Table 3; Fig. 4a), and a significant inverse correlation between neuronal density in the lateral septal nucleus and disease duration in patients with major depressive disorder $P = 0.037$, $r = -0.90$; Table 3; Fig. 4b). No significant correlations were found between neuronal density in the lateral septal nucleus and lithium dosage ($P = 0.37$, $r = 0.37$; Table 3) or antidepressant dosage (for 90 days) in patients with bipolar disorder ($P = 0.86$; $r = -0.11$, Table 3).

Discussion

To our knowledge, this is the first quantitative assessment comparing the neuronal density of the septal nuclei in patients with schizophrenia, bipolar disorder, and major depressive disorder and in matched control subjects. A significant decrease in neuronal density in the lateral septal nucleus of bipolar patients was found without accompanying changes in the mean cross-sectional area of this nucleus in comparison with control subjects. Furthermore, no significant differences were found in the neuronal density (mm^3) of the medial and lateral cell groups

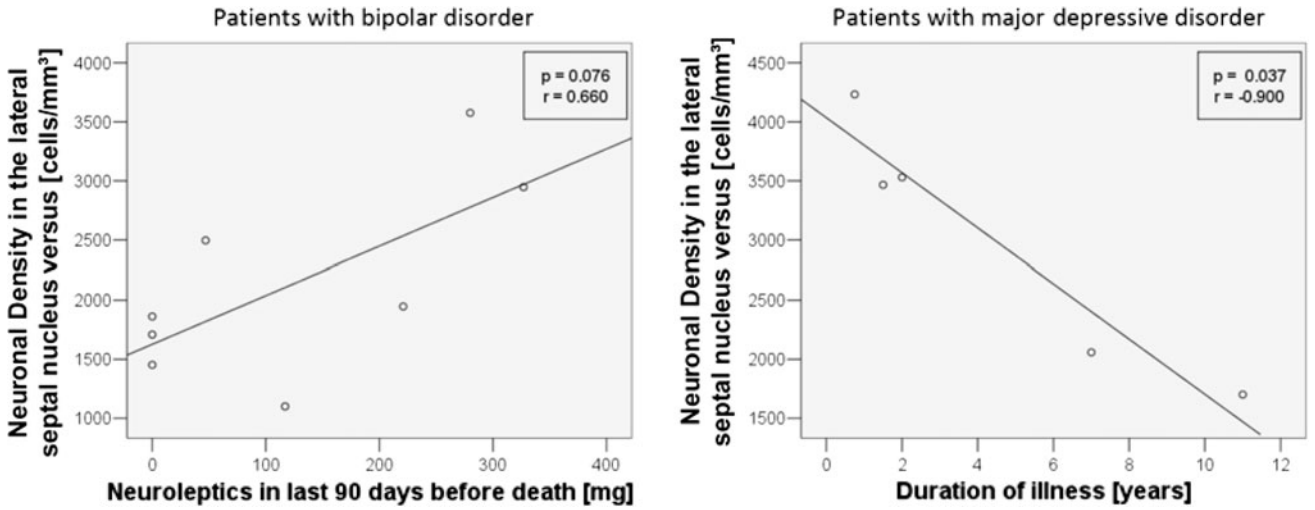

Fig. 4 Spearman correlations between neuronal density in the lateral septal nucleus (mm^3) and typical neuroleptics in the last 90 days before death (mg) in patients with bipolar disorder (**a**) and correlations between neuronal density in the lateral septal nucleus ($mm^{3)}$ and duration of disease (years) in patients with major depressive disorder (**b**)

between patients with schizophrenia or major depressive disorder and control subjects.

The mean cross-sectional area of the lateral septal nuclei did not differ among patients with schizophrenia, bipolar disorder, and major depressive disorder and the control subjects.

A volumetric study showed that the septal tissue did not differ between the patients with schizophrenia or affective disorders and the control subjects [27].

The decrease in neuronal density seen in the lateral septal nucleus points to circumscribed pathology in those areas of the septal tissue located next to the lateral ventricles and may indicate more generalized periventricular disturbances in patients with bipolar disorder.

A limitation of this study was the small sample size of patients with bipolar disorder and major depressive disorder. Despite this limitation, the difference in the neuronal density in the lateral septal nucleus of patients with bipolar disorder compared with control subjects was significant ($P = 0.013$). Another constraint of this study is the increased possibility for a false positive result due to the multiple testing. Nevertheless, the prior work by Sheehan et al. [2] indicated the involvement of the lateral septal nucleus in affective disorders. Several neuroimaging and histopathological studies of brain regions in patients with affective disorders have shown that these disorders are accompanied by alterations not only at the macroanatomical, but also at the microanatomical levels. Volumetric and structural abnormalities have been observed in the corpus callosum, adhesio interthalamica, gray matter, white matter, lateral and third ventricles, hippocampus, amygdala, basal ganglia, frontal, temporal and cingulate cortices, thalamus, and cerebellum of patients with bipolar disorder [28–31]. Even so, some of these findings were not confirmed by other groups. Ventricular enlargement, decreased amygdala volumes, and reduced hippocampal volumes have all been found in patients with major depressive disorder [32–36]. In the limbic and cortical areas, significant cellular alterations in patients with affective disorders have also been reported. Reduced neuronal density in the limbic and prefrontal regions might be implicated in the pathology of bipolar disorder [37]. A reduction in the number of nonpyramidal neurons in layer II of the anterior cingulate cortex [38, 39] and in the hippocampus (CA2) [40] as well as decreased neuronal density in layers III, V, VI of the anterior cingulate cortex [41] and in the lateral nucleus of the amygdala [42] have been reported in patients with bipolar disorder. Increased neuronal density in layer VI of the anterior cingulate cortex [43] with no changes in the neuronal density in the anterior cingulate cortex [44] or the Heschl's gyrus [45] were found in patients with bipolar disorder. In contrast, no changes in the neuron number in the subgenual prefrontal cortex were reported in patients with bipolar disorder or major depressive disorder [46]. A reduction in the size of neurons in layer I of the orbitofrontal cortex [47] and in pyramidal neurons of the hippocampus (CA1) of bipolar patients [48] has been reported in patients with bipolar disorder. The density of nonpyramidal neurons was decreased in layer II of the anterior cingulate cortex in patients with bipolar disorder [38]. Moreover, decreased neuronal size in the lateral amygdalar nucleus [49], the anterior cingulate cortex [44] and the orbitofrontal cortex [47], increased neuron numbers in the mediodorsal, anteroventral, and anterodorsal thalamus [50], and increased neuronal density in the hippocampus [51] have all been reported in patients with major depressive disorder. The lateral septal region receives afferent connections from the hippocampus,

the entorhinal cortex, the medial part of the amygdala, the nucleus interpenduculais of the stria terminalis, and the lateral part of the hypothalamus and sends efferent connections through the fornix to the hippocampus, the entorhinal cortex, the medial part of the amygdala, and the nucleus accumbens [52]. The lateral septal region integrates cognitive information from the prefrontal cortex, the entorhinal cortex, and the hippocampus, with affective information from the amygdala, the hypothalamus, the habenula, and the bed nucleus and then transmits that integrated information to the diencephalon and mesencephalon [2, 52], which are structures that may play an important role in the pathophysiology of affective disorders [2]. The lateral septal nuclei and their connections to the hippocampus and hypothalamus are responsible for the control of emotional responses [2]. The medial septal nuclei have connections through the fornix to the hippocampus, the dentate gyrus and the entorhinal cortex [53] and are involved in exploratory behavior [54]. The medial septal nuclei are the main output of the septal region, whereas the lateral septal nuclei are the main input of the septal region [55]. Neuronal changes have also been reported in the dorsal raphe nucleus, the hypothalamus, and the habenula in affective disorders [56–62]. Abnormalities in the hypothalamic–pituitary–adrenal axis (HPA axis) have also been implicated in patients with bipolar disorder [63, 64]. The HPA-axis is a major component of the stress system and is involved in suicidal behavior [65, 66]. Stress might contribute to neuronal atrophy in the hippocampus. Stress causes a reduction in the BDNF mRNA in the hippocampus of rats compared with control rats [67].

The eight patients with bipolar disorder investigated in our study received typical neuroleptics in the 90 days preceding death and showed only a trend toward a positive correlation between typical neuroleptic doses and neuronal density in the lateral septal nucleus (see Table 3; Fig. 4a). This trend, however, might be due to the small sample size of these patients.

Postnatal neurogenesis in the caudate nucleus and the nucleus accumbens of rats has been reported [68], and neuronal plasticity has been shown in the septum of adult rats [69].

A few studies have found lower c-Fos-like immunoreactivity, a marker of neuronal activation, in the lateral septal nucleus of mice and rats in learned helplessness, an established animal model of clinical depression [70, 71]. Various reports have also found that proteins such as brain-specific kinase, brain-derived neurothrophic factor (BDNF) and anti-apoptotic protein Bcl-2, which are involved in neurogenesis, are located in the lateral septal nucleus and subventricular zone of humans and rats [72–74]. Several studies have demonstrated that typical and atypical neuroleptics have neurotrophic effects via pCREB (phosphorylated cyclic AMP response element binding protein) and BDNF (brain-derived neurotrophic factor) in animal models [75–80]. In patients with bipolar disorder, therefore, typical neuroleptics could potentially affect secondary messenger intracellular systems, such as pCREB and BDNF, which are involved in neurogenesis and neuroplasticity in the lateral septal nucleus, to compensate for the cell loss inherent in the disease.

In summary, our study demonstrated the presence of a significantly reduced neuronal density in the lateral septal nucleus in patients with bipolar disorder compared with control subjects, suggesting focal pathology in an important limbic region involved in emotions.

This abnormality could be a structural correlate to the emotional disturbances displayed by patients with bipolar disorder. A significant negative correlation between neuronal density in the lateral septal nucleus and the duration of disease in major depressive disorder was also found, indicating that neurogenesis is disrupted in affective disorders.

The absence of neuronal atrophy of the septal nuclei in patients with schizophrenia further supports an early neurodevelopmental abnormality in the etiology of schizophrenia, which has been demonstrated in earlier studies [81, 82]. A limitation of this study is the shrinkage of the septal nuclei, which may influence the results. If the septal nuclei are subject to shrinkage, any systematic error would occur randomly in the postmortem brains of control subjects and the patients with schizophrenia, bipolar disorder, and major depressive disorder [27, 83]. Another constraint of this study is the use of a cell size measurement based on 2-D-measurements (two dimensions) because the irregular shape of the neurons may influence the results. The study by Liu et al. [48], however, also applied a cell size measurement based on 2-D-measurements.

The research presented herein suggests that disrupted neuronal plasticity underlies the neuropathology of bipolar disorder, which is characterized by deficits in the lateral septal nucleus, an important limbic relay structure between the subcortical and cortical regions.

Acknowledgments This study was supported by the Stanley Foundation and NBL-3/BMBF (Förderkennzeichen 01ZZ0407).

Conflict of interest statement All authors declare that they have no conflict of interest.

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