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ORIGINAL PAPER

A postmortem assessment of mammillary body volume, neuronal number and densities, and fornix volume in subjects with mood disorders

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Abstract Mammillary bodies are relay nuclei within limbic and extralimbic connections. Whereas other subcortical brain structures have been found to be altered in depression, no current information exists regarding the pathomorphology of mammillary bodies in affective disorders. We studied the postmortem brains of 19 human subjects with mood disorders (9 with major depressive disorder and 10 with bipolar I disorder) and 20 control individuals and assessed the mammillary body and fornix volumes, number of neurons and neuronal densities. We found that male control subjects have significantly larger mammillary bodies compared with females. In addition, control subjects of both sexes with the diagnosis/cause of death of "heart failure/insufficiency" had significantly smaller mammillary body volumes compared with non-psychiatric patients who died from other causes. When estimating the mammillary bodies volumes of patients with depression compared with control subjects, a significant reduction of the left mammillary body volume was found in patients with bipolar disorder, but not in patients with major depression. However, significant depression-associated mammillary body volume reductions were found between the control subjects who did not die of heart failure and patients with major depression and bipolar disorder. Moreover, the MB volumes of control subjects who died of heart failure were in the range exhibited by subjects with depression. There was no significant influence of suicidal behavior on mammillary volumes observed. Moreover, no significant group differences in the total neuronal number or neuronal density were found between the controls, subjects with major depression and subjects with bipolar disorder. Furthermore, the fornix volumes were significantly reduced only in the control subjects with heart failure. Taken together, these results show that the mammillary bodies are compromised in depression.

Keywords Mammillary bodies · Fornix · Major depression · Bipolar disorder · Morphometry

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Introduction

In the past decade, considerable progress has been made with regard to revealing the neural substrates that underlie mood disorders. Neuroimaging and postmortem studies have demonstrated the prominent role of fronto-subcortical pathomorphology in major depressive disorder (MDD) involving the ventral prefrontal cortex, striato-pallidal nuclei, mesiotemporal brain structures, thalamus and other brain stem areas, which support neurocircuitry-based rat models in which both the functional and structural brain pathology play important roles in the development of mood disorders [1–10]. These neural networks consist of the medial prefrontal cortex and other closely related areas in the medial and caudolateral orbital cortex, amygdala, hippocampus and ventromedial parts of the basal ganglia, where alterations in the gray matter volume are found. In particular, evidence from lesion studies suggests that the medial prefrontal cortex and related limbic and striato-

pallido-thalamic structures organize emotional expression. In bipolar disorder (BP), the most consistent findings include preservation of the total cerebral volume with regional gray and white matter structural changes in the prefrontal, midline and limbic networks, ventriculomegaly and white matter hyperintensities (for recent detailed overviews on the neuropathology of mood disorders, see [11–13]). Thus, these limbic structures play important roles in both MDD and BP.

The mammillary bodies (MB) are important relay nuclei within limbic and extralimbic connections. They are a pair of small round bodies located on the undersurface of the brain, constituting the principal component of the posterior hypothalamus. The MB are composed of several nuclei, each having distinct connections. The MB nuclei receive information from the hippocampus and are reciprocally connected to the anterior thalamic nuclei, septum and midbrain [14–16]. The functional importance and strategic positioning of the MB, which links the temporo-limbic to the cortico-thalamic brain structures, make them an ideal candidate brain structure to study the alterations that occur in affective disorders. Interestingly, while numerous other subcortical brain structures, including the hypothalamic nuclei, have been morphometrically analyzed in depression [3, 17–21], there is no current information regarding the potential pathomorphology of the MB in mood disorders. Thus, we performed a postmortem study of the volume, neuronal number and neuronal density of the MB in subjects with mood disorders and in control individuals. In addition, we analyzed the fornix volumes in a subgroup of the subjects with depression and controls.

Materials and methods

Subjects

All of the brains were obtained from the New Magdeburg brain collection. The case recruitment, acquisition of personal data, performance of autopsy and handling of autoptic material were conducted in strict accordance with the Declaration of Helsinki and were approved by the Ethical Committee of Magdeburg. In addition, written consent was obtained from the next-of-kin. Moreover, the information for clinical diagnoses was obtained from clinical records and/or structural interviews of physicians involved in the subjects' treatment or was obtained from relatives [3].

The brains of 19 human subjects (7 men and 12 women; mean age: 50.3 ± 12.1 years) with mood disorders as diagnosed according to the DSM-IV (9 with major depressive disorder, MDD; 10 with bipolar I disorder, BD) and of 20 control individuals (8 men and 12 women; mean age: 48.0 ± 9.3 years) without a history of neuropsychiatric disorder were investigated. None of the patients or control subjects had a history of substance abuse or alcoholism. Neuropathological changes due to neurodegenerative or traumatic processes were ruled out by an experienced neuropathologist as previously described [3]. (For demographical, histological, clinical and psychopharmacological treatment details, please refer to Tables 1, 2 and 3.)

Tissue processing

The subjects' brains were removed within 4–72 h after death 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 sectioning anterior to the genu and posterior to the splenium of the corpus callosum. After embedding all of the brains in paraffin, serial coronal sections of the middle block were cut (20 μm) and mounted. The distance between the sections was 1 mm. The shrinkage factor caused by the fixation and embedding of the brains was calculated as described previously [17, 18]. The mean volume shrinkage factor for patients with schizophrenia, patients with affective disorder and controls was 2.21. There were no significant differences in the shrinkage factors among the three groups (MDD, BP and controls), and every 50th section was Nissl and myelin stained (Heidenhain/Woelke).

Morphometric analysis

MB planimetry

The MB were assessed using the delineation criteria as previously described [15]. The morphometric analysis was performed by one of the coauthors (M.K.), who was blind to the diagnosis. The measurements of the cross-sectional areas of the structure were performed by planimetry from fourfold magnifications of the sections as previously described [3]. The structural volumes were calculated by multiplying the cross-sectional areas by the distance between the sections and by adding the volumes obtained from this calculation along the entire rostro-caudal axis of the respective structure. The structural volumes in the fixed brain were determined by multiplying the measured volumes of the respective structures in the paraffin block by the individual shrinkage factors for each brain. All of the slides were coded, so that the investigators (M.K., H.-G.B.) were blind to the subjects' diagnosis during the analysis. To establish the inter-rater reliability, measurements of

Table 1 Characteristics of control cases

Individuals without mood disorder (controls)	Age (years)	Gender	Cause of death	Number of episodes (depressive/manic)	Postmortem delay (hours)
1	40	m	Heart failure	0	96
2	38	m	Myocardial infarction	0	19
3	56	m	Cardiac insufficiency, acute renal failure	0	30
4	46	m	Heart failure	0	24
5	39	m	Cardiac and circulatory insufficiency	0	4
6	64	m	Rupture of aortic aneurism, nephrolithiasis	0	35
7	47	m	Acute respiratory failure	0	24
8	54	m	Pulmonary embolism, Ulcus duodeni	0	24
9	66	f	Heart failure	0	24
10	61	f	Heart failure	0	24
11	67	f	Heart failure	0	24
12	38	f	Heart failure	0	24
13	64	f	Myocardial infarction	0	26
14	63	f	Myocardial infarction	0	24
15	39	f	Heart failure	0	48
16	33	f	Ruptured aortic aneurism, arteriosclerosis,	0	72
17	48	f	Status asthmaticus	0	48
18	50	f	Ruptured aortic aneurism	0	72
19	48	f	Pulmonary embolism	0	26
20	30	f	Pulmonary embolism, Marfan syndrome	0	48

seven brains were performed by two investigators (M.K., H.-G.B.). The inter-rater reliability was 0.93, and the test–retest reliability (M.K.) was sufficient with the intercorrelation coefficients (0.98). The whole brain volume (V) was calculated by dividing the fresh brain weight (Bw) obtained during the autopsy by the specific brain weight ($F = 1.037$): V (ml) = Bw (g)/F.

MB neuron counts

The section thickness after the histological procedures was 18.9 ± 1.0 μm (mean ± SD). A counting grid was used to demarcate a three-dimensional box within the thickness of the section as previously described [16] and to create at least 4-μM guard zones at the top and bottom of each section, which enabled for sufficient three-dimensional counting. Twelve outlined boxes per left and right MB were counted, and the boxes were scattered in a random manner over the entire MB visual field. The inter-rater reliability was approximately 0.92. The product of the volume and neuronal density was used to determine an estimate of the total neuronal number.

Due to the small size of the structure, only four sections per brain could be used to estimate the total MB volume and total neuronal number.

Fornix volume determination and delineation criteria

The fornix volumes were determined for a subset of the patients. We investigated 10 control cases without heart failure, four subjects with heart failure, four subjects with MDD and four subjects with BD. These cases were randomly selected from the MB groups, and the fornix morphometry was performed as previously described [7]. The difference between the anterior and posterior poles was used to calculate the length of the fornix. In addition, the areas of the fornix were separately measured by planimetry of the serial sections for the right and left hemisphere. The sections were then scanned with a digital microscope camera (Polaroid, USA), and the Digitrace© software program was used to calculate the cross-sectional areas of the fornix. The distance between the sections was 1 mm.

The volumes were calculated by interpolation and integration across all of the measured core areas. The volume shrinkage (resulting from paraffin embedding) and the thickness of the slices were controlled by previously described methods [22]. The shrinkage correction was determined by multiplying the tissue volume with the shrinkage factor for each individual brain. The anterior boundary of the fornix was the anterior commissure, and the posterior boundary was the hippocampus. The corpus

Table 2 Characteristics of subjects with depression

Individuals mood disorder	Age (years)	Gender	Cause of death	Number of episodes (depressive/manic)	Postmortem delay (hours)
Unipolar					
1	35	m	Suicide	2/0	15
2	36	m	Suicide	1/0	42
3	61	f	Cardiac insufficiency	11/0	70
4	63	f	Pulmonary embolism	2/0	17
5	39	f	Suicide	?	48
6	53	f	Suicide	2/0	47
7	46	f	Suicide	?	48
8	26	f	Suicide	?	22
9	53	f	Suicide	?	46
Bipolar					
10	69	m	Heart failure	4/4	24
11	39	m	Heart failure	14/14	56
12	47	m	Suicide	3/3	24
13	42	m	Suicide	4/11	17
14	39	m	Myocardial infarction	1/1	14
15	65	f	Pulmonary embolism	10/1	14
16	46	f	Suicide	3/3	4
17	62	f	Pulmonary embolism	11/11	72
18	60	f	Pulmonary embolism	7/6	14
19	59	f	Suicide	16/3	72

callosum was used as the superior boundary, and the thalamus was used as the inferior boundary.

Statistical analysis

Multivariate analysis of covariance was performed for the diagnosis, each side of the brain (i.e., left and right hemisphere) was an independent variable (repeated measures), and the whole brain volume was a covariate. The effects sizes were determined for the 3-group comparisons (MDD, BD and controls), and post hoc Tukey–HSD tests were performed to detect group differences. The fornix volume data were analyzed using pairwise t-tests and were followed by the familywise post hoc Fisher′s LSD test. The confounding variables including whole brain volume were primarily tested on normality using the Kolmogorov–Smirnov test. The fixation and postmortem delay showed significant deviations from normality (KS-Z 1.8, $P = 0.003$, KS-Z 1.56, $P = 0.015$). Therefore, the group comparisons for the fixation times and postmortem delay were performed using the non-parametric Jonckheere–Terpstra test. The Spearman's correlation coefficient rank tests were performed to determine the effects of the postmortem delay, time of fixation, illness duration, number of illness episodes and psychotropic medication (i.e., antidepressants, neuroleptics, benzodiazepines and lithium) on the volume data. In addition, a special emphasis was placed on suicidal behavior and heart failure/insufficiency as potential confounding factors.

Results

Qualitative observations

A neuroanatomical overview of the right and left sides of the MB is given in Fig. 1. The dashed line represents the delineation used for the MB volume studies. No overt differences were found between the MDD, BD patients and control cases.

Quantitative estimates

MB volumes

First, we compared the left and right MB volumes of the female and male control cases. We found that men have significantly larger MB than women (left MB in men, 36.9 ± 7.0 mm^3; in women, 25.5 ± 4.8 mm^3; $P = 0.004$; right MB in men, 32.4 ± 7.0 mm^3; in women, 23.3 ± 5.0 mm^3; $P = 0.011$). These results obtained from an individual sample population were consistent with our previous

Table 3 Psychopharmacological treatment

Individuals mood disorder	AD (AE)	N (CE)	BDZ	CBZ	Li
Unipolar					
1	0	0	0	0	0
2	0	0	0	0	0
3	30	111	16.5	0	0
4	50	0	0	0	0
5	93	0	3.1	0	560
6	67	0	0	0	0
7	124	109	0	0	0
8	0	0	0	0	0
9	0	0	0	0	0
Bipolar					
10	0	0	1.6	0	280
11	28	0	0	0	740
12	95	47	18.3	0	565
13	0	110	17.6	0	0
14	0	280	0	0	0
15	93	117	3.9	0	0
16	133	327	3.3	0	558
17	0	110	17.6	0	0
18	52	109	10.9	0	0
19	112	0	10	600	0

All medications are given as mean daily dose over the last 90 days prior to death [3]

AD antidepressants, *AE* amitriptyline equivalents, *BZD* benzodiazepines, *CBZ* carbamazepine, *CE* chlopromazine equivalents, *DE* diazepam equivalents, *Li* lithium, *N* neuroleptics

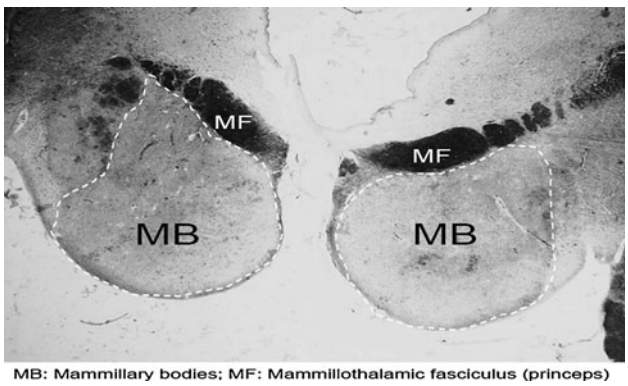

Fig. 1 Low power microphotograph showing left and right human mammillary bodies of a control case (combined stain for Nissl and myelin after Heidenhain/Woelke) and the dashed line indicates the delineation for MB volume studies

finding of gender differences in the MB volumes in psychiatrically healthy individuals [15]. We then sought to determine whether the diagnosis of "heart failure/insufficiency" had any influence on the MB volumes (prompted by the findings of a previous MRI study [22]) and showed that this

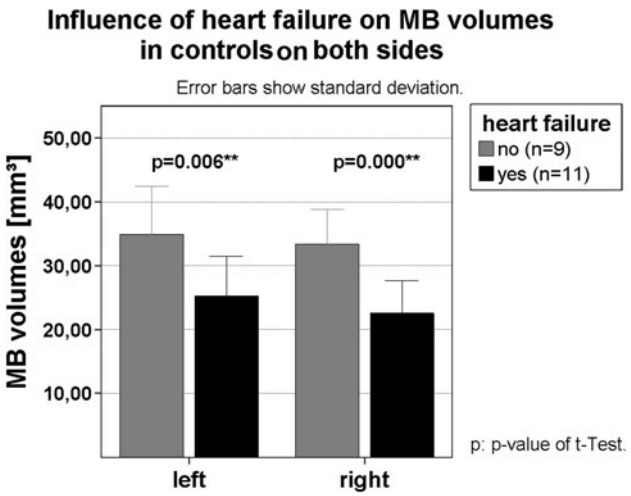

Fig. 2 Influence of heart failure on MB volumes

was indeed the case. We found that both male and female control subjects with heart failure/insufficiency had significantly smaller right MB volumes than non-psychiatric patients who died from other causes (left side: $P = 0.006$; right side: 0.000; Fig. 2). Next, we estimated the MB volumes of patients with depression compared with control subjects. We found that the BD, but not MDD patients, exhibited a significant reduction in the left MB volumes, compared with control subjects (cases with and without heart failure) ($P = 0.021$, Fig. 3). We also found that the volume reduction was much more pronounced in the male subjects with mood disorders than in females (data not shown). Interestingly, the male patients with depression (MDD and BD) demonstrated larger MB volumes than females with the same diagnoses, although this finding did not reach significance. Interestingly, when determining whether the individuals had died from heart failure, it became apparent that significant depression-associated MB volume reductions occurred only between the control subjects who had died from other causes and depressed patients (left MB: MDD vs. controls: $P = 0.029$; BD vs. controls: $P = 0.002$; right MB: MDD vs. controls: $P = 0.010$; BD vs. controls: $P = 0.001$; Fig. 4). The MB volumes of the control subjects who died of heart failure were within the range of the subjects with depression. No significant influence of suicidal vs. non-suicidal behavior was observed on the MB volumes. Furthermore, no correlation was found between the MB volumes and the age of the patients, postmortem delay, duration of illness and medication taken by the patients.

Total number of MB neurons

We found a gender difference in the number of neurons in the control subjects. The control male subjects had a significantly higher number of MB neurons than the female

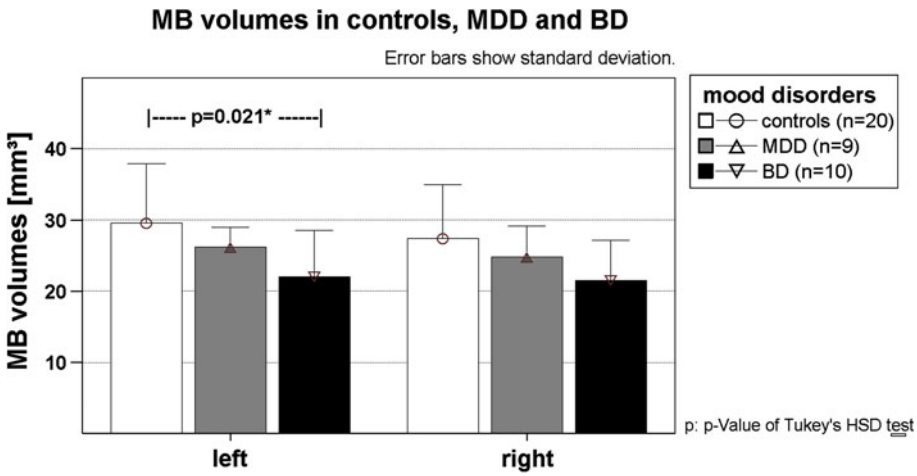

Fig. 3 MB volumes in controls, MDD and BD

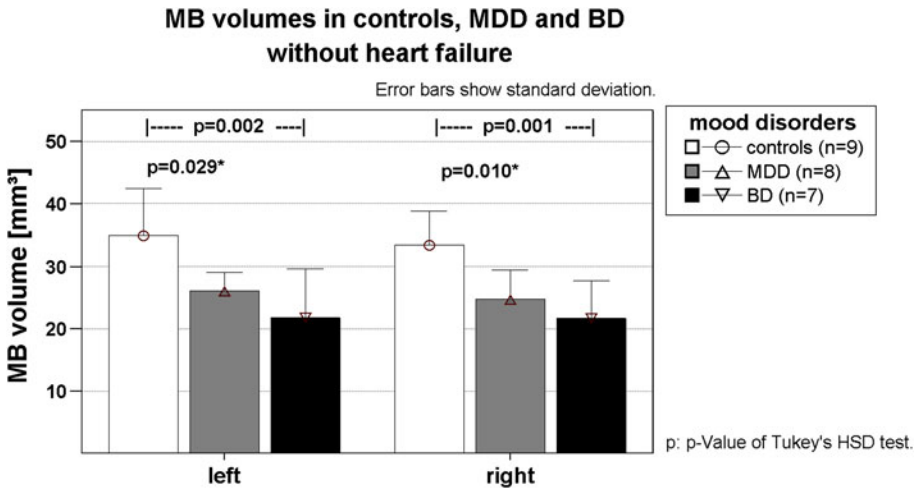

Fig. 4 MB volumes in controls, MDD and BD without heart failure

control subjects on the right side ($P = 0.049$; Fig. 5). No significant group differences were found between the controls and MDD and BD patients (Fig. 6). The estimated total number of neurons did not significantly differ between the subjects with heart failure and those who died from other causes.

MB neuronal densities

No significant gender differences were found in the neuronal densities in the control subjects and patients with depression. There was also no group difference observed between the MDD and BD patients in their neuronal densities. However, the control subjects with heart failure had significantly reduced neuronal densities compared with the MDD patients (right side only; $P = 0.001$; Fig. 7). The age, time of autolysis, brain weight, time of fixation, medication, duration of illness and suicidal behavior had no significant influence on the MB volume, neuronal number and neuronal densities.

Fornix volumes

Familywise statistical analysis employing the Fisher′s LSD test revealed that in normal subjects with heart failure, the fornix volumes were significantly reduced on both sides ($P = 0.049$ on the left side and $P = 0.023$ on the right side), compared with subjects who had suffered from MDD. In individuals with BD, a strong tendency toward a reduction in the fornix volumes was found ($P = 0.81$ on the left side; $P = 0.61$ on the right side; Fig. 8).

Limitations of the study

A clear limitation of this study was the small number of brains used to estimate the fornix volumes. Thus, further

studies with larger cohorts are clearly needed. In addition, another caveat might be that among the suicidal cases, there might have been some patients who had suffered from heart disease.

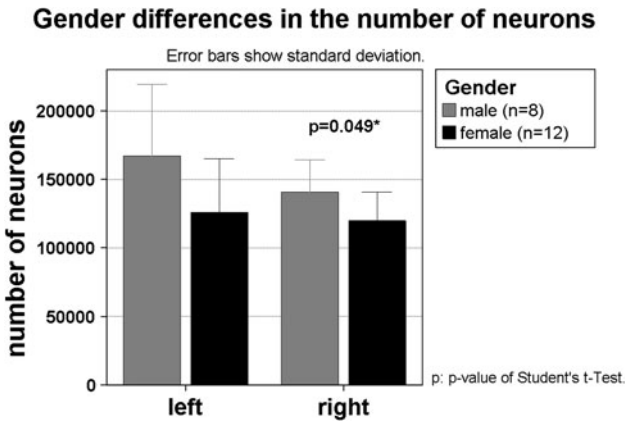

Fig. 5 Gender differences in the number of neurons (controls)

Discussion

We showed that significant disease-associated MB volume reductions occurred in patients with major depression and bipolar disorder. Thus, we found that the neuropathological changes of the MB that are associated with mood disorders substantially differed from previous studies that described effects observed in schizophrenia [15]. However, reduced MB volumes are not unique to depression. Typically, MB volume deficits can be found in chronic alcoholics who suffer from Korsakoff′s syndrome and/or Wernicke′s encephalopathy. However, MB volume shrinkage can also be found in many chronic alcoholics in the absence of amnesia or dementia [24, 25]. Because the structural MB changes in depression are very similar to those observed in severe alcoholism, we specifically excluded patients with a known history of alcohol abuse (depressive patients and controls) from this study. Interestingly, the MB shrinkage also occurred in patients with obstructive sleep apnea and,

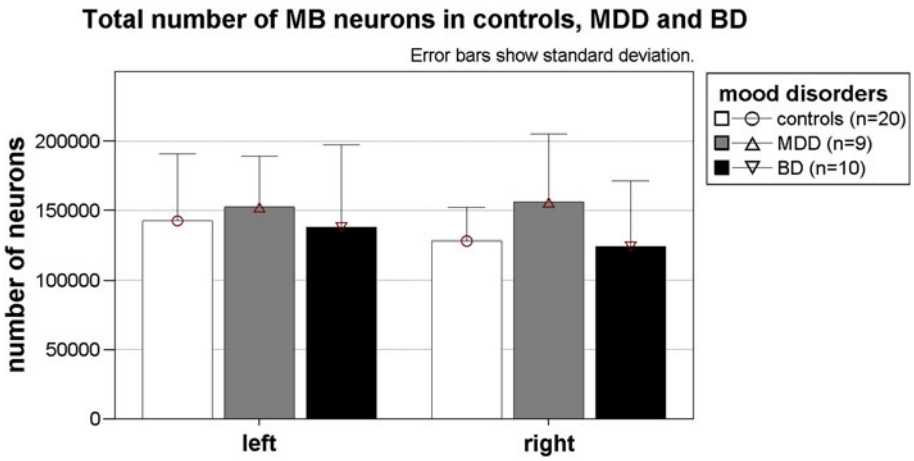

Fig. 6 The total number of neurons in controls, MDD and BD

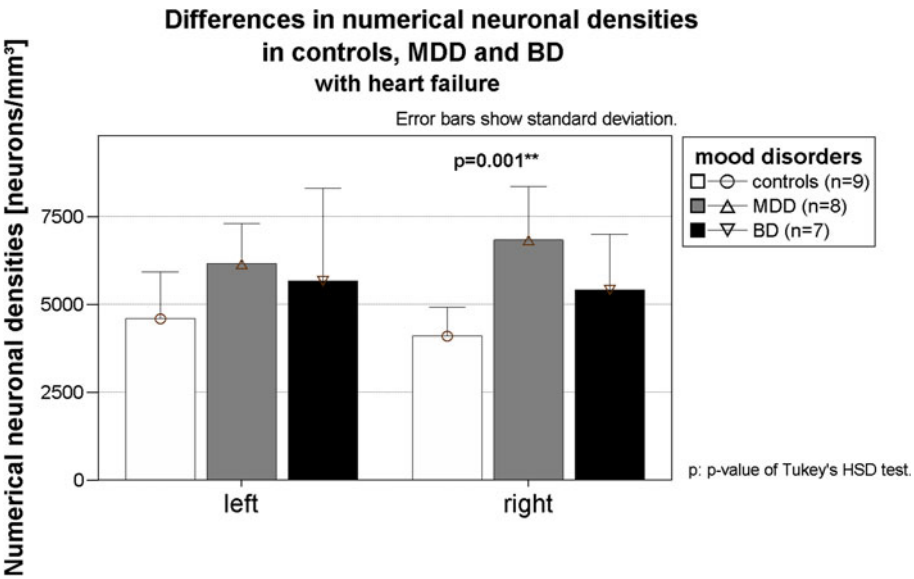

Fig. 7 Differences in the numerical density in controls with heart failure, MDD and BD

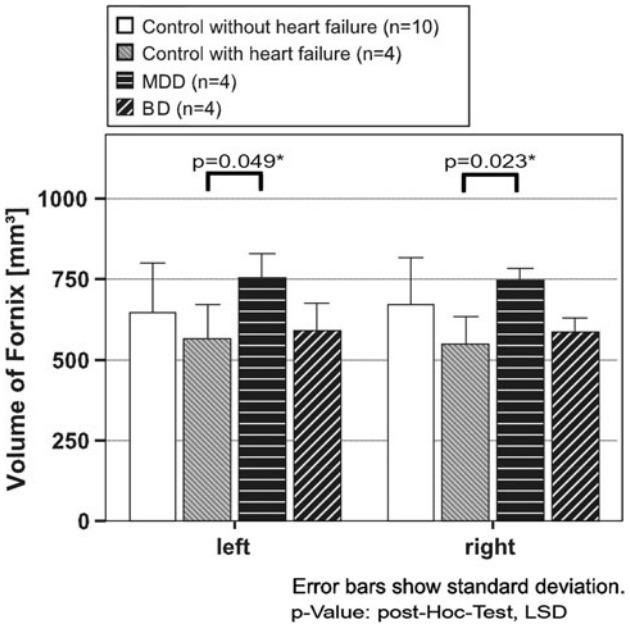

Fig. 8 Fornix volumes in controls with and without heart failure, MDD and BD

more importantly for our study, in patients with cardiac and acute liver failure [23, 26, 27]. Based on the findings of two previous studies, we focused our data analysis on the potential relationship between heart disease and MB volumes/neuronal number. Consistent with previous findings obtained by Kumar and colleagues [23], we found that "heart failure/insufficiency" can influence MB volume. We observed that both male and female control subjects with heart failure/insufficiency demonstrated significantly smaller MB volumes than the non-psychiatric patients who died from other causes. Because a previous report had shown that heart failure can be accompanied by regional gray matter volume loss in other brain areas [28], we determined that heart failure might be an important, yet clearly underestimated, caveat in postmortem brain morphometric studies, which warrants additional consideration as a potential confounding factor. Because the number of neurons was not reduced in the subjects with depression, the observed shrinkage should have occurred largely at the expense of the MB neuropil, which was consistent with what has been reported in studies of severe alcoholism or in cases of surgical removal of the colloid cysts from the third ventricle [29]. Because affective disorders have been increasingly acknowledged as astroglial deficit disorders, and reduced astroglial density has been reported for different brain regions in depression (summarized by [30, 31] and others), decreased astroglial package density might contribute to the observed neuropil reduction. We are currently investigating this specific hypothesis by performing GFAP and glutamine synthetase immunocytochemical studies.

Furthermore, fornix damage or malformation may significantly affect the volume of the MB neuropil, because the fornix is the main afferent system of the hippocampus, connecting it to the septal nuclei and hypothalamic mammillary bodies. It has been established that in depression, the stress-induced dysregulation of the hypothalamic–pituitary–adrenal axis leads to numerous structural and physiological alterations in the hippocampus, including volume reduction, changes in adult neurogenesis, decreased expression of corticoid receptors and modifications in the expression levels of specific genes such as brain-derived neurotrophic factor and the cAMP response element reviewed in [32]. It is possible that a structurally and functionally compromised hippocampus may influence the MB integrity through their afferent systems, namely the fornix. Furthermore, experimental studies have elegantly demonstrated that a complete unilateral fornix transection in monkeys and the unilateral hippocampal/subicular loss in humans both result in a 50% reduction of the mammillary body volume (data reviewed in [28]). In our initial report on fornix volumes in controls and patients with depression, we could not find a reduction in the fornix volumes in patients with affective disorder [7]. In this study, we showed that the control subjects with heart failure have significantly smaller fornix volumes than the MDD cases. In addition, the BD subjects also exhibited a strong tendency toward reduced fornix volumes. Thus, MB shrinkage may be associated with a reduced fornix volume. Consistent with the involvement of the fornix in the pathomorphology of BD, a recent study reported that adolescent subjects with BD showed lower fornical fractional anisotropy than the control subjects [33]. In addition, a recent MRI study showed that control subjects with and without heart failure exhibited significant differences in fornix cross-sectional areas, which corresponded to a reduced MB volume [23]. In this study, we estimated that the average fornix volume in control subjects with cardiac failure was reduced by 14 percent on the left side and by 18 percent on the right side, compared to controls without cardiac failure. Although these differences were not significant between the two groups, slightly reduced fornix volumes in cases with heart failure might influence the MB volume [23]. In subjects with MDD, however, we observed reduced MB volumes, but normal fornix volumes. Thus, besides the fornix, other connections may also contribute to MB pathomorphology in depression. For example, the impairment of another major input to the MB, a projection from the ventral tegmental Gudden′s nucleus and other tegmental nuclei to the MB may influence their pathomorphology [16, 34, 35]. The hippocampus and other limbic structures such as Gudden′s nucleus, via its connections to the MB, significantly contribute to episodic memory, novel learning and spatial memory in humans

(reviewed in [16, 34, 35]). Because disturbances of episodic memory are important facets of the behavioral abnormalities spectra observed in both MDD and BD (for recent reviews, see [36–38]), and impairments in spatial learning and memory are also frequently diagnosed in individuals with depression [38], it is conceivable that MB neuropathology significantly contributes to the impairment of memory and emotional processes [38–40] in mood disorders. Lastly, MB are reciprocally connected to the anterior thalamus through the mammillo-thalamic tract. Profound memory deficits in Wernicke′s encephalopathy are largely due to disturbances of functional mammillo-thalamic connectivity [41]; however, whether this important fiber system is compromised in depression remains to be elucidated.

Conflict of interest The authors declare that they have no conflict of interests.

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