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ORIGINAL PAPER

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Volume deficits of subcortical nuclei in mood disorders

A postmortem study

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Abstract Structural changes in subcortical nuclei may underlie clinical symptoms of mood disorders. The goal was to determine whether macrostructural changes exist in brain areas assumed to be involved in regulation of mood and whether such changes differ between major depressive disorder and bipolar disorder. A case-control design was used to compare volumes of all major subcortical nuclei. Brains of patients with major depressive disorder (n = 9) or bipolar disorder (n = 11) or of individuals without a neuropsychiatric disorder (n = 22) were included. Exclusion criteria were a history of substance abuse or histological signs of neurodegenerative disorders. Volumes of the striato-pallidal nuclei, of the hypothalamus, thalamus, amygdala, hippocampus and basal limbic forebrain were determined in the right and left hemisphere by planimetry of 20 μm whole brain serial paraffin sections. Comparisons between patients with bipolar disorder, major depressive disorder and controls showed a significant ($\Lambda = 0.35$, $F_{20,56} = 1.93$, $P = 0.028$) overall difference in volumes of all investigated regions with strong effect sizes ($f > 0.40$) contributed by the hypothalamus, external pallidum, putamen and thalamus. As compared to controls, a strong effect size ($f > 0.40$) was found in the bipolar group for smaller volumes of the hypothalamus, external pallidum, putamen and thalamus, whereas in patients with major depressive disorder a strong effect size was only found for a smaller volume of the external pallidum. In conclusion our data suggest that pathways presumably involved in mood regulation have structural pathology in affective disorders with more pronounced abnormalities in bipolar disorder.

Key words mood disorders · morphometry · subcortical nuclei · postmortem

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Introduction

In recent years several neuroimaging studies and some postmortem studies indicated fronto-subcortical pathomorphology in mood disorders involving ventral prefrontal cortices (Drevets et al. 1997; Ongür et al. 1998; Hirayasu et al. 1999; Rajkowska et al. 1999, 2001; Bremner et al. 2002), striato-pallidal nuclei (Husain et al. 1991; Krishnan et al. 1992; Aylward et al. 1994; Baumann et al. 1999; Beyer et al. 2004), mesiotemporal structures (Sheline et al. 1996, 1998, 1999; Strakowski et al. 1999, 2002; Bremner et al. 2000; Mervaala et al. 2000; Frodl et al. 2002a, 2002b, 2003, 2004; Blumberg et al. 2003; Hastings et al. 2004) and the thalamus (Dupont et al. 1995; Dasari et al. 1999). In post-stroke depression a similar regional pattern of pathology has been described (Herrmann et al. 1995; Vataja et al. 2001). Together with data from animal experiments and functional neuroimaging studies those results have led to neuroanatomic models of mood regulation which emphasize the relevance of limbic-

striato-pallidal-thalamo-cortical circuits (Soares and Mann 1997; Baumann and Bogerts 1999; Vawter et al. 2000).

Pathology of subcortical gray structures such as the diencephalon and the striato-pallidal nuclei could explain subtle enlargement of ventricles in mood disorders, although ventricular enlargement appears to be less consistent than in schizophrenia (Iacono et al. 1988; Elkis et al. 1995; Baumann et al. 1997). Reduced volumes of the striato-pallidal nuclear complex have been reported in depression (Husain et al. 1991; Krishnan et al. 1992; Parashos et al. 1998). Divergent results were reported for bipolar disorder (Strakowski et al. 1999, 2002; Beyer et al. 2004). However, given the functional complexity of the basal ganglia (Alexander et al. 1986; Nakano et al. 2000) and their connectivity with thalamic nuclei, more comprehensive studies including all subcortical structures are needed.

Recently, several neuroimaging studies indicated structural abnormalities that affected differentially brain regions in major depressive disorder (MDD) and bipolar disorder (BPD). In MDD volume reductions have been reported for the amygdala (Hastings et al. 2004) and for the core nucleus with no differences for the total amygdala (Sheline et al. 1998), whereas other studies found enlarged volumes for this nucleus in BPD (Strakowski et al. 1999, 2002; Altshuler et al. 1998). However, also a reduction of amygdala volume in bipolar patients has been found (Blumberg et al. 2003) and an enlargement in first-episode patients with MDD (Frodl et al. 2003). Divergent results between mood disorders have been described for thalamic volumes (Dupont et al. 1995) and for the number of neurons in the locus coeruleus (Baumann et al. 1999). As of now, to our knowledge no study determined structural pathology in both mood disorders simultaneously to reinvestigate the reported hyper-normal structural pattern of some nuclei in BPD in contrast to MDD (Baumann and Bogerts 2001).

In the present study we used volumetric measurements of serial postmortem sections with combined Nissl-myelin staining to investigate the assumed subtle structural pathology in striatal-pallidal basal ganglia, diencephalic and limbic structures comparing patients with unipolar major depressive or bipolar mood disorder to healthy controls. Based on models indicating putative pathways involved in regulation of mood we hypothesised structural changes in these pathways in mood disorders. Structural pathology in these brain systems may be a substrate for some of the clinical symptoms in mood disorders.

Materials and methods

Subjects

Brains of 20 human subjects (8 males, 12 females) with mood disorders according to DSM-IV (major depression n = 9, 2 males, 7 females, bipolar I disorder n = 11, 6 males, 4 females) and of 22 control individuals (8 males, 14 females) without a history of neuropsychiatric disorder were investigated. Nine subjects with mood disorders died of natural causes, the other eleven patients were suicide victims.

The study was performed in compliance with policies of the ethic committee of the University of Magdeburg and written consent was obtained from the next-of-kin. Information for clinical diagnoses was obtained by the careful study of clinical records and/or by structured interviews of physicians involved in treatment and persons who either lived with or had frequent contact with the subjects before death. Final Axis I diagnoses (DSM-IV) were assigned in consensus meetings of two psychiatrists using all available information from interviews and clinical charts. None of the patients or controls had a history of substance abuse, since this was one of the exclusion criteria. Qualitative neuropathological changes due to neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Pick's disease), tumours, inflammatory, vascular (microangiopathy, infarctions, lacunar infarctions, Binswanger's disease) or traumatic processes were ruled out by two experienced neuropathologists (L. G., C. M.). For demographical, histological, clinical and psychopharmacological data see Tables 1 and 2.

Morphometry

For volumetric analysis of subcortical structures, serial coronal paraplast sections with a thickness of 20 µm and a combined Nissl- and myelin-staining were used. Histologic and morphometric procedures were performed, as previously described by us in detail (Baumann et al. 1999). Briefly, entire brains were fixed in 4 % paraformaldehyde for at least 3 months and, after separation of the brainstem, divided by coronal cuts into three bihemispherical coronal blocks comprising the frontal lobe anterior to the genu of the corpus callosum (anterior block), the fronto-temporo-parietal lobe extending over the whole length of the corpus callosum (middle block) and the occipital lobe (posterior block). The middle block included, beside the cortical areas, all investigated subcortical gray structures; these are the striato-pallidal basal ganglia (caudate, putamen, nucleus accumbens, external and internal pallidum), the diencephalon (thalamus, hypothalamus), the basal limbic forebrain (substantia innominata, islands of Calleja, olfactory tubercle), the amygdala and the hippocampal formation.

After paraplast embedding, all blocks were cut into serial whole brain sections and each 50th section was stained with a combined Myelin(Heidenain-Wölcke or luxol fast blue)-Nissl staining resulting in a section distance of 1 mm. Due to the relative short rostro-caudal extension of the nucleus accumbens, we chose each 25th section in the area of this nucleus resulting in an intersectional distance of 0.5 mm. The use of these inter-section distances yielded a coefficient of error for all structures in the 0.01–0.04 range. Shrinkage of brain tissue during paraffin embedding was evaluated for each brain by calculating the ratio of identical distances between opposite cortical gyri on the most rostral and the most caudal section of the middle block before and after embedding. Individual volume shrinkage factors (VSF) were calculated from the measured linear factor (LSF) by the formula $VSF = (LSF)^3$. Mean shrinkage factor was 2.17 for control brains, 2.20 for MDD patients and 2.14 for bipolar patients (ANOVA with the three groups as independent variable n. s.). For volumetry of subcortical structures, every Nissl-myelin stained section of the middle block was analysed.

Delineation criteria

Criteria for delineation of subcortical gray structures in coronal sections are illustrated in Fig. 1.

Basal ganglia

Caudate, putamen, nucleus accumbens, external and internal pallidum were delineated as described previously (Baumann et al. 1999) (see Fig. 1b–d).

Diencephalon – hypothalamus

The hypothalamus was measured as the gray mass lateral to the third ventricle below the hypothalamic sulcus. As the rostral marker we used the middle point of the rostro-caudal extent of the optic chiasm. The hypothalamus was delineated up to the caudal end of the mammillary bodies. Laterally it was bordered by the basal limbic forebrain (see Fig. 1f–m).

Diencephalon – thalamus

The thalamus represents the largest subcortical structure and exhibits a complex architecture. The borders of the thalamus have been frequently defined for the human and are readily distinguishable (Dewulf 1972). Thalamic delineation included the entire thalamus except for the lateral geniculate body and was performed according to the criteria of Hirai and Jones (1989) (Fig. 1h–t).

Limbic regions – amygdala

The amygdala including its cortical parts was delineated from the most rostral to the most caudal extent and could be macroscopically clearly distinguished from the hippocampus and delineated from the medial temporal cortex (Fig. 1f–m).

Limbic regions – hippocampal formation

Measurements of the hippocampal formation were delineated like described previously (Bogerts et al. 1985) (Fig. 1j–u).

Limbic regions – basal limbic forebrain

The basal limbic forebrain (BLF) included the following anatomical structures: parts of the substantia perforata, ventral amygdalofugal fibres, islands of Calleja and the substantia innominata (Fig. 1f–i). It was delineated as the basal gray mass bordered laterally by a line from the temporal invagination point to the ventral-most point of the border between the external pallidum and the putamen. The medial border of the BLF was taken by the hypothalamus, the superior border by the anterior commissure and the basal ganglia. As the rostral and caudal border of the BLF, we defined the most rostral or the most caudal section, respectively, where the anterior commissure was visible.

Planimetry

Measurements of cross-sectional areas of the structures were performed by planimetry from 4-fold magnifications of the sections. Structure volumes were calculated by multiplying cross sectional areas by the distance between the sections and adding up volumes obtained by this procedure along the entire rostro-caudal axis of the re-

Table 1 Characteristics of patients and controls

Patients					
Patient no./ sex/age/ age at onset, y	Brain weight, g	Postmortem delay, h	Cause of death	Number of episodes depressed/manic[c]	Psychiatric diagnosis[a] (DSM-IV-TR)
1/f/53/51	1280	47	Suicide by electrocution	2/0	Major Depression 296.33
2/f/39/n.a.[b]	1400	48	Suicide by overdose of medication	n.a./0	Major Depression 296.23
3/f/46/n.a.	1410	48	Suicide by hanging	n.a./0	Major Depression 296.24
4/f/63/n.a.	1120	17	Pulmonary embolism	2/0	Major Depression 296.34
5/f/61/50	1240	70	Bronchopneumonia	11/0	Major Depression 296.34
6/f/53/n.a	1340	46	Suicide by hanging	n.a./0	Major Depression 296.33
7/f/26/n.a	1320	22	Suicide by jumping	n.a./0	Major Depression 296.33
8/m/35/33	1240	15	Suicide by stabbing	2/0	Major Depression 296.33
9/m/36/35	1568	42	Suicide by hanging	1/0	Major Depression 296.34
45.8 ± 12.7	1324 ± 128	39.4 ± 18.0			
10/m/47/38	1670	24	Suicide by stabbing	3/3	Bipolar I Disorder Depressed 296.53
11/f/46/33	1300	4	Suicide by overdose of medication	10/1	Bipolar I Disorder Depressed 296.54
12/m/42/26	1320	17	Suicide by hanging	4/11	Bipolar I Disorder Depressed 296.54
13/f/62/51	1300	72	Pulmonary embolism	11/11	Bipolar I Disorder Depressed 296.54
14/f/60/50	1140	15	Bronchopneumonia	7/6	Bipolar I Disorder Depressed 296.54
15/m/39/37.5	1520	14	Pulmonary embolism	1/1	Bipolar I Disorder Mixed 296.62
16/f/59/35	1274	72	Suicide by overdose of medication	16/3	Bipolar I Disorder Depressed 296.54
17/m/39/25	1590	56	Myocardial infarction	14/14	Bipolar I Disorder Manic 296.44
18/m/69/43	1300	48	Pulmonary embolism	6/11	Bipolar I Disorder Manic 296.44
19/m/69/51	1320	24	Cardiac insufficiency	4/4	Bipolar I Disorder Depressed 296.54
20/f/65/40	1449	52	Cardiac insufficiency	23/19	Bipolar I Disorder Depressed 296.54
54.3 ± 11.8	1380 ± 157	36.1 ± 24.6			
Mean ± SD: 50.5 ± 12.7 yrs.	Mean ± SD: 1355 ± 144	Mean ± SD: 37.6 ± 21.4			

[a] At time of death none of the patients was in a remitted state. Most recent episode prior to decease is specified
[b] "n.a." indicates not exactly available
[c] patient 15 had 1 mixed episode

Table 1 *Continued*

Controls			
Patient no./ sex/age (yrs.)	Brain weight, g	Postmortem delay, h	Cause of death
1/f/48	1170	48	Acute asthmatic attack
2/m/40	1550	70	Myocardial infarction
3/m/64	1310	35	Cardiac insufficiency
4/f/48	1200	26	Pulmonary embolism
5/f/30	1500	48	Pulmonary embolism
6/f/38	1200	24	Pulmonary embolism
7/f/61	1350	24	Cardiac insufficiency
8/f/67	1210	25	Sudden cardiac death
9/f/63	1050	24	Sudden cardiac death
10/f/39	1210	24	Heat stroke after sun exposure
11/f/50	1055	72	Rupture of aortal aneurysm
12/m/54	1430	24	Pulmonary embolism
13/m/47	1450	24	Myocardial infarction
14/f/52	1200	24	Cardiac insufficiency
15/m/47	1200	24	Respiratory insufficiency
16/f/64	1190	24	Sudden cardiac death
17/f/33	1150	72	Myocardial infarction
18/m/38	1550	19	Rupture of aortal aneurysm
19/f/64	1260	26	Myocardial infarction
20/m/39	1405	4	Sudden cardiac death
21/m/46	1295	24	Sudden cardiac death
22/f/66	1150	24	Pulmonary embolism
Mean ± SD: 49.9 ± 11.6	Mean ± SD: 1276 ± 148	Mean ± SD: 34.5 ± 21.5	

Table 2 Psychopharmacological treatment

Case-No.	AD (AE)	N (CE)	BDZ (DE)	CBZ	Li
1	67	0	0	0	0
2	93	0	3.1	0	560
3	124	109	0	0	0
4	50	0	0	0	0
5	30	111	16.5	0	0
6	0	0	0	0	0
7	0	0	0	0	0
8	0	0	0	0	0
9	0	0	0	0	0
10	20	0	0	0	0
11	133	327	3.3	0	558
12	95	47	18.3	0	565
13	0	110	17.6	0	0
14	52	109	10.9	0	0
15	0	280	0	0	0
16	112	0	10	600	0
17	0	221	0.8	0	740
18	0	0	6.8	0	0
19	0	0	1.6	0	280
20	93	117	3.9	0	0

AD antidepressants; *AE* amitriptyline equivalents; *BZD* benzodiazepines; *CBZ* carbamazepine; *CE* chlopromazine equivalents; *DE* diazepam equivalents; *Li* lithium; *N* neuroleptics. All medications are given as mean daily dose over the last 90 days prior to death

spective structure. Volumes of the structures 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.

Investigators were blind for names and diagnosis of the subjects. To establish interrater reliability, measurements of 10 brains were performed by two investigators (R. S., B.Ba.). Interrater reliability was sufficient for all structures, ranging from 0.85 (hypothalamus) to 0.97 (basal ganglia). Test-retest reliability (R. S.) also proved sufficient with intercorrelation coefficients ranging from 0.89 (hypothalamus) to 0.98 (basal ganglia).

Whole brain volume (V) was calculated by dividing the fresh brain weight (Bw) obtained during autopsy by specific brain weight (F = 1.037): V (ml) = Bw (g)/F.

Statistical analyses

Multivariate analysis of covariance was performed with diagnosis and side, i. e. left and right hemisphere, as independent variables (repeated measures) and whole brain volume as a covariate. Following MANCOVA, effect sizes (f) for group differences were calculated to identify nuclei that most contributed to the overall difference (Stevens 1990). Effect sizes were determined for 3-group comparisons (i. e. major depressive disorder, bipolar disorder, controls) and 2-group contrasts (mood disorders, controls).

ROI variables, i. e. volume data of single nuclei, and confounding variables including whole brain volume were primarily tested on normality by use of the Kolmogorov-Smirnov test. Only times of fixation and postmortem delay showed significant deviations from normality (KS-Z 1.8, $P = 0.003$, KS-Z 1.56, $P = 0.015$). Group comparisons for fixation times and postmortem delay were performed by use of the Jonckheere-Terpstra test. Spearman's correlation coefficient rank tests were carried out to investigate effects of postmortem delay, time of fixation, illness duration, number of illness episodes, and psychotropic medication (i. e. antidepressants, neuroleptics, benzodiazepines and lithium) on volume data.

Results

Diagnostic groups, i. e. major depressive disorder, bipolar disorder and control subjects, did not differ significantly in whole brain volume, age, gender and brain shrinkage factors ($F = 1.87$, $df = 2,39$, $P = 0.17$; $F = 1.28$, $df = 2,39$, $P = 0.29$; $F = 1.11$, $df = 2,39$, $P = 0.34$, $F = 0.05$, $df = 2,39$, $P = 0.95$, respectively), nor in postmortem delay or times of fixation ($JT = -0.02$, $P = 0.98$, $JT = -1.24$, $P = 0.22$). However, whole brain volumes were significantly correlated with volumes of all single structures investigated in this study (all r_p-values > 0.34, all P-values < 0.025). Therefore, whole brain volume was included as covariate in the analysis.

Three-group comparisons

The 3 groups showed significantly different overall regional volumes as hypothesised (λ [Wilks lambda] = 0.35, $F_{20,56} = 1.93$, $P = 0.028$). Differences between groups for the following regions contributed large

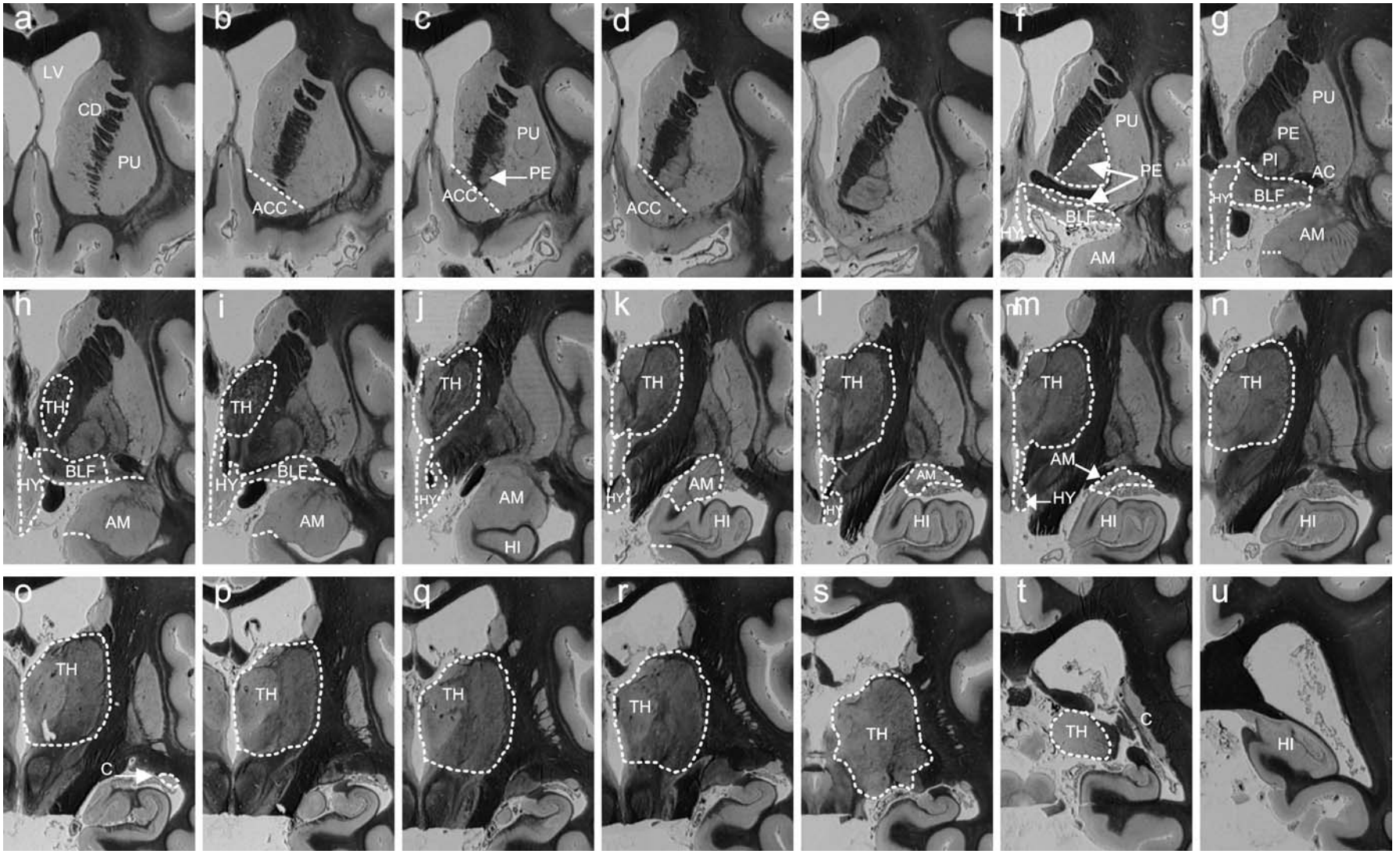

Fig. 1 Delineation criteria of the measured subcortical nuclei in coronal serial Nissl-myelin stained sections. CD (candate): **a–t**, PU (putamen): **a–s**, ACC (nucleus accumbens): **b–d**, PE (external pallidum): **c–o**, PI (internal pallidum): **g–h**, AM (amygdala): **f–m**, HI (hippocampus): **j–u**, HY (hypothalamus): **f–m**, TH (thalamus): **h–t**, BLF (basal limbic forebrain): **f–i**. For detailed explanation see text

effects ($f > 0.40$) to the overall difference: hypothalamus, external pallidum, thalamus and putamen (see Fig. 2). The remaining six structures showed medium effect sizes ($f > 0.25$) (see Table 3). No significant interaction was found for group (diagnosis) and brain side.

Major depressive disorder vs controls

Bilateral univariate ANOVAs of patients versus controls showed the only large effect in major depressive disorder for the external pallidum (Fig. 2), and medium effect sizes for the hypothalamus, the amygdala, the basal limbic forebrain and the nucleus accumbens.

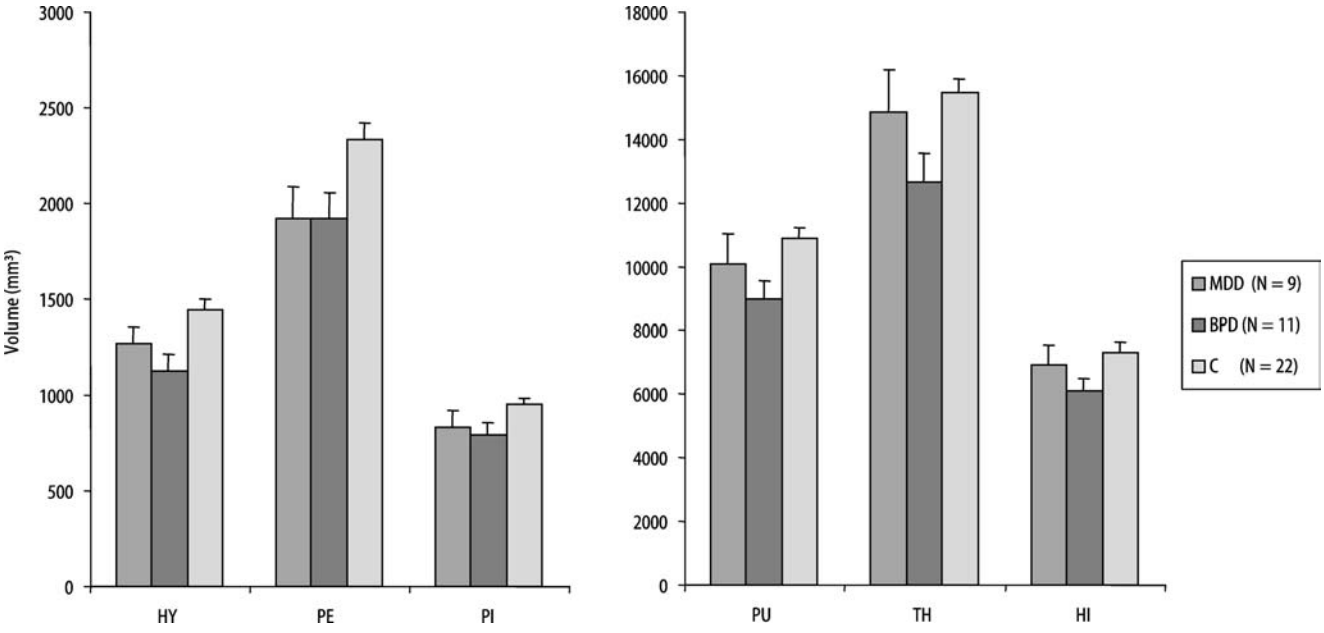

Fig. 2 Volumes of structures mostly reduced in patients with major depressive disorder or bipolar disorder. Volumes are corrected for whole brain volumes and given as the sum of right and left structures. For abbreviations see Fig. 1 and Table 3

Table 3 Volumes of subcortical structures in patients with mood disorders and in control subjects

A: Data

Region	MDD (N = 9)			BPD (N = 11)			C (N = 22)		
	total	left	right	total	left	right	total	left	right
Basal ganglia									
nucleus accumbens	1087±483	535±284	551±223	1031±470	503±246	528±245	1240±502	615±253	625±266
caudate	8405±2393	4134±1168	4270±1230	7873±2280	3932±1101	3940±1186	8657±1764	4305±899	4351±872
putamen	9858±3421	4776±1889	5082±1786	9503±2425	4693±1099	4810±1338	10565±2010	5263±995	5302±1031
pallidum externum	1942±671	966±314	976±360	2068±566	1011±232	1057±338	2248±542	1095±280	1153±272
pallidum internum	837±327	411±154	426±177	839±267	417±127	422±144	925±156	455±72	471±90
Diencephalon									
thalamus	14942±5086	7402±2480	7540±2631	13396±3793	6653±1905	6744±1896	15035±2349	7534±1249	7501±1113
hypothalamus	1276±362	644±184	631±181	1191±315	605±162	586±162	1410±302	705±137	705±167
Limbic structures									
amygdala	2765±853	1365±404	1400±454	2964±514	1491±258	1474±267	3077±537	1581±263	1496±303
hippocampus	6959±2312	3377±1146	3581±1180	6432±1253	3065±579	3367±701	7115±1755	3435±897	3680±877
basal limbic forebrain	1160±422	580±198	580±248	1269±437	629±223	641±224	1385±450	703±239	681±231
Added structures									
basal ganglia	22620±6987	11242±3406	11378±3594	21314±5784	10556±2654	10758±3138	23635±4456	11733±2196	11902±2276
diencephalon	16218±5414	8047±2644	8171±2794	14587±4057	7258±2026	7330±2039	16445±2575	8239±1346	8206±1243
limbic system	10884±3422	5323±1685	5561±1745	10666±1944	5184±916	5482±1059	11577±2402	5720±1212	5857±1202
subcortical grey	50694±15593	25076±7615	25619±7991	46567±11519	22998±5424	23569±6119	51657±8960	25692±4536	25965±4444
brain weight (g)	1324±128			1380±157			1284±149		

Table 3 *Continued*

B: Analyses

Region	MDD vs BPD vs C[1]			BPD vs C[2]			MDD vs C				BPD vs MDD			
	Effect Size			Diff. i. %	Effect Size		Diff. i.%	Effect Size			Diff. i.%	Effect Size		
Basal ganglia														
nucleus accumbens	0.37			−16.9	0.35		−12.3	0.29			−5.2	0.15		
caudate	0.32			−9.1	0.31		−2.9	0.14			−6.3	0.25		
putamen	0.43			−10.1	0.48		−6.7	0.20			−3.6	0.28		
pallidum externum	0.48			−8.0	0.45		−13.6	0.45			6.5	0.03		
pallidum internum	0.38			−9.3	0.40		−9.5	0.28			0.2	0.17		
Diencephalon														
thalamus	0.42			−10.9	0.49		−0.6	0.11			−10.3	0.40		
hypothalamus	0.54			−15.5	0.56		−9.5	0.36			−6.7	0.26		
Limbic structures														
amygdala	0.37			−3.7	0.28		−10.1	0.36			7.2	0.02		
hippocampus	0.34			−9.6	0.36		−2.2	0.15			−7.6	0.26		
basal limbic forebrain	0.33			−8.4	0.24		−16.2	0.32			9.4	0.00		
Added structures														
basal ganglia	0.42			−9.8	0.44		−4.3	0.23			−5.8	0.26		
diencephalon	0.44			−11.3	0.51		−1.4	0.13			−10.1	0.40		
limbic system	0.37			−7.9	0.38		−6.0	0.26			−2.0	0.18		
subcortical grey	0.44			−9.9	0.48		−1.9	0.17			−8.1	0.34		

B: Analyses

Region	MDD vs BPD vs C[1]			BPD vs C[2]				MDD vs C				BPD vs MDD			
	Effect Size	F-value	P-Value	Diff. i. %	Effect Size	F-value	P-Value	Diff. i.%	Effect Size	F-value	P-Value	Diff. i.%	Effect Size	F-value	P-Value
Basal ganglia															
nucleus accumbens	0.37	2.86	0.07	−16.9	0.35	4.11	0.05	−12.3	0.29	2.49	0.13	−5.2	0.15	0.40	0.54
caudate	0.32	2.04	0.14	−9.1	0.31	3.16	0.09	−2.9	0.14	0.62	0.44	−6.3	0.25	1.22	0.29
putamen	0.43	3.81	**0.03***	−10.1	0.48	7.66	**0.01****	−6.7	0.20	1.21	0.28	−3.6	0.28	1.54	0.22
pallidum externum	0.48	4.88	**0.01***	−8.0	0.45	6.56	**0.02***	−13.6	0.45	6.31	**0.02***	6.5	0.03	0.02	0.89
pallidum internum	0.38	3.01	0.06	−9.3	0.40	5.25	**0.03***	−9.5	0.28	2.36	0.14	0.2	0.17	0.59	0.46
Diencephalon															
thalamus	0.42	3.77	**0.03***	−10.9	0.49	7.77	**0.01****	−0.6	0.11	0.37	0.55	−10.3	0.40	3.22	0.09
hypothalamus	0.54	6.05	**0.01***	−15.5	0.56	10.32	**0.003****	−9.5	0.36	4.03	0.06	−6.7	0.26	1.38	0.26
Limbic structures															
amygdala	0.37	2.83	0.07	−3.7	0.28	2.57	0.12	−10.1	0.36	4.02	0.06	7.2	0.02	0.01	0.93
hippocampus	0.34	2.41	0.10	−9.6	0.36	4.22	**0.05***	−2.2	0.15	0.70	0.41	−7.6	0.26	1.33	0.26
basal limbic forebrain	0.33	2.26	0.12	−8.4	0.24	1.90	0.18	−16.2	0.32	3.19	0.09	9.4	0.00	0.00	0.97
Added structures															
basal ganglia	0.42	3.59	**0.04***	−9.8	0.44	6.29	**0.02***	−4.3	0.23	1.55	0.22	−5.8	0.26	1.29	0.27
diencephalon	0.44	4.10	**0.02***	−11.3	0.51	8.51	**0.01****	−1.4	0.13	0.54	0.47	−10.1	0.40	3.14	0.10
limbic system	0.37	2.94	0.07	−7.9	0.38	4.77	**0.04***	−6.0	0.26	2.06	0.16	−2.0	0.18	0.65	0.43
subcortical grey	0.44	3.97	**0.03***	−9.9	0.48	7.45	**0.01***	−1.9	0.17	0.89	0.35	−8.1	0.34	2.15	0.16

MDD major depressive disorder; *BPD* bipolar disorder; *C* control subjects; absolute volumes in mm^3 given as mean ± SD

[1] ANCOVA with 3-level diagnosis factor and side (repeated measures) as independent variable and brain weight as covariate. No significant interaction of side and diagnosis was seen.

[2] ANCOVA with 2-level diagnosis factor and side (repeated measures) as independent variable and brain weight as covariate. Trend for side diagnosis interaction in thalamus and hypothalamus.

* significant P-value

Bipolar disorder vs controls

The bipolar group showed large effects for the same regions that exhibited large effects in 3-group comparisons, and medium effects for all other regions except the basal limbic forebrain (Fig. 2). In all 2-group comparisons, patients showed smaller regional volumes than controls.

Bipolar disorder vs major depressive disorder

Direct contrasts between both patient groups demonstrated a trend toward a large effect for the thalamus ($f > 0.40$), and medium effect sizes for the putamen, the hypothalamus and the hippocampus. All these structures showed smaller volumes in the bipolar group.

When ROI variables were corrected for whole brain volumes, post hoc LSD tests provided essentially similar results for 2-group comparisons as univariate ANCOVAs. Although there were no significant gender differences between the three groups in this study, groups were not entirely matched for gender. Therefore a 3 x 2 factorial ANCOVA with whole brain volume as the covariate and diagnosis and sex as between subject factors was performed but did not change the results.

Confounding variables

Linear correlation analyses yielded no significant effect on regional volumes of postmortem delay (r_s-values between –0.25 and –0.006 for patients and between –0.37 and 0.01 for controls, all P-values > 0.09) and times of fixation (r_s-values between –0.37 and –0.05 for patients and between –0.35 and –0.06 for controls, all P-values > 0.10). In the patient groups, none of the ROIs exhibited significant corrrelations with illness duration or psychotropic drug exposure. The mean illness duration was 5.0 years in MDD and 15.2 years in BPD. There was a significant difference between the groups (t-test, $p = 0.006$). Bipolar patients had a higher mean number of affective illness episodes (16.6, t-test, $p = 0.026$) compared to unipolar patients (3.6). No difference was found for depressive episodes between the groups.

In brains of bipolar patients, significant negative correlations, however, were seen for hippocampal volumes on both sides with the sum of manic and depressive episodes ($r_s = –0.74$, $P = 0.01$ [left], $r_s = –0.77$, $P = 0.005$ [right]) and with the number of depressive episodes separately ($r_s = –0.62$, $P = 0.04$ [left], $r_s = –0.68$, $P = 0.02$ [right]). A negative correlation with number of depressive episodes was also found for the volumes of the amygdala reaching significance level only for the right side ($r = –0.60$, $P = 0.05$ [left], $r = 0.72$, $P = 0.01$ [right]). In unipolar patients, significant correlations were observed between regional volumes and number of depressive episodes for the external and internal pallidum, the thalamus and the hypothalamus (all $r = –0.89$, $P = 0.04$).

Discussion

According to our hypothesis, measurement of subcortical volumes in mood disorders revealed deficits of structures belonging to limbic-striato-pallidal-thalamo-cortical pathways presumably regulating mood, namely the external pallidum, the putamen, the thalamus and the hypothalamus. However, the 2-group comparisons showed that only in subjects with bipolar disorder did these structures contribute a strong effect to the overall group difference, whereas in major depressive disorder only the external pallidum showed a strong effect. Therefore, the most important result of our study is the predominant affection of patients with bipolar disorder.

Confounding effects of histological procedures on volume measurements in this study are unlikely since times of postmortem delay and tissue fixation did not correlate with volumes of brain structures and did not differ between the groups. Moreover shrinkage of tissue due to paraffin embedding was controlled in each single case by determining individual shrinkage factors.

Our finding of a structural deficit of striato-pallidal basal ganglia is of important physiological relevance when it is considered that volume changes of a certain structure reflect long-term alterations in the functional state of this region. It has been proposed that in particular limbic-affiliated basal ganglia circuits including ventral parts of the striatum and pallidum, the mediodorsal thalamus and the prefrontal cortex are affected in mood disorders (Baumann et al. 1999; Vawter et al. 2000). Alterations at each point of those circuits will have consequences for the entire network. The result of reduced size of basal ganglia is in agreement with MRI studies in major depressive disorder (Husain et al. 1991; Krishnan et al. 1992), but not in subjects with bipolar disorder (Aylward et al. 1994; Strakowski et al. 1999, 2002). However, in the current study the mean age of bipolar patients was 54.3 years. A decreased volume of basal ganglia structures in bipolar subjects is a different finding than previous studies conducted with younger samples. Aylward et al. (1994) found a larger caudate in male bipolar patients (mean age 39.3 years), while Strakowski et al. (1999) found a larger globus pallidus and striatum in BPD (mean age 27 years). Strakowski et al. (2002) reported that the putamen was significantly larger in first-episode patients and nearly significant larger in multiple-episode patients than in healthy controls. In this study the mean subject ages were 22 years for the first-episode patients and 25 years for the multiple-episode patients. Brambilla and colleagues reported an inverse correlation between age and left putamen volumes in bipolar patients (Brambilla et al. 2001). Since the subjects' mean age in the above-mentioned studies was younger than our subjects' mean age, our sample had an overall later age of onset. Interestingly, a more recent study in older adults with BPD (mean age 58.8 years) found decreased caudate volumes (Beyer et al. 2004). These findings, together with our results, suggest

that bipolar patients may have more pronounced age-related effects in basal ganglia structures compared to healthy individuals. Moreover, some psychotropic drugs such as neuroleptics and lithium are believed to increase subcortical, in particular caudate nucleus volumes (Chakos et al. 1994; Moore et al. 2000). Thus, investigation of bipolar patients differing in those confounding variables might have led to different results. In the current study 9 patients received neuroleptics in the last 3 months prior to death and 5 patients had medication with lithium; however, neuroleptics and lithium showed no influence on basal ganglia volumes in these patients. Diagnostic groups showed no significant differences in age at the time of death. This indicates that in our sample of bipolar patients without a relevant history of lithium intake (only 4 of 11 bipolar patients) or neuroleptic treatment (bipolar patients received only low amounts of neuroleptics, see Table 2) volumes of striato-pallidal basal ganglia are reduced. Taken together, our data clearly show that striato-pallidal volumes are smaller in mood disorders, with a diagnostic focus on BPD and a structural focus on the external pallidum.

As of now few studies exist comparing volumes of subcortical structures in BPD and MDD directly. Structural and functional neuroimaging and postmortem studies found no differences between those two affective illnesses in the subgenual cortex, a small part of the anterior cingulate cortex in subjects with familiar MDD or BPD. Volumes, perfusion and numbers of glia cells in this region were reduced in both disorders (Drevets et al. 1997, 1998; Ongür et al. 1998). Considering previous neuroimaging studies on bipolar disorder and major depressive disorder we expected differences for volumes of the amygdala and the thalamus with a reduction in MDD (Sheline et al. 1998; Hastings et al. 2004; Dupont et al. 1995) and an increase in BPD (Strakowski et al. 1999, 2002). According to those data, volumes of the amygdala showed medium effect size for a reduction in major depressive disorder compared to controls, but volumes of the amygdala and the thalamus in bipolar subjects were even smaller than in the other groups. Since differences between first episode patients and patients with recurrent depression for the amygdala are reported (Frodl et al. 2003), possible influences of illness duration on the results have to be considered. In our study the mean illness duration was 5.0 years in MDD and 15.2 years in BPD. The results of the current postmortem study are therefore difficult to compare with MRI studies which investigated first-episode patients or patients with a shorter illness duration. However, in our study none of the ROIs exhibited significant correlations with illness duration.

In the present study, smaller hypothalamic volumes contributed the strongest effect to the overall difference between groups. This indicates tissue loss and can be interpreted as an anatomical substrate of HPA dysregulation in mood disorders. In recent years, the hypothalamus and hippocampus attracted increased interest with regard to the effects of stress on neurobiological systems in individuals with mood disorders. Clinical, physiological and postmortem studies demonstrated a dysregulation of the HPA axis at the hypothalamic level (Holsboer and Barden 1996; Raadsheer et al. 1995; Purba et al. 1996; Bernstein et al. 1998, 2002). As in Cushing syndrome, neurotoxic effects of increased glucocorticoid levels were assumed to be a possible cause for hippocampal volume reductions in several psychic disorders including posttraumatic stress disorder (Driessen et al. 2000) and major depression (Sapolsky 2000). Hippocampal volumes reductions were found in bipolar patients but contributed only medium effects to the overall group difference. This is in disagreement with studies showing smaller volumes in major depressive disorder (Sheline et al. 1996; Bremner et al. 2000; Mervaala et al. 2000; Steffens et al. 2000; Frodl et al. 2002), but consistent with negative reports (Axelson et al. 1993; Coffey et al. 1993; Ashtari et al. 1999; Vakili et al. 2000). However, negative reports using MRI (Coffey et al. 1993; Axelson et al. 1993) did not separate the hippocampus from the amygdala. Different demographic characteristics of the subjects included in the MRI studies such as age, gender, race and number of depressive episodes might explain the divergent results. Furthermore our result of decreased hippocampal volumes in patients with BPD is in accordance with one study (Blumberg et al. 2003), but in conflict with literature data showing negative results (Strakowski et al. 1999; Hauser et al. 2000). The latter MR study, however, used 5 mm thick sections and therefore has methodological limitations. Moreover, the study of Strakowski and colleagues (1999) involved subjects with a much smaller number of illness episodes which might explain the discrepant results. Our result of a negative correlation of the number of manic and depressive episodes in bipolar patients, which corresponds to a reported correlation between length of depressive episodes and hippocampal volumes in major depressive disorder (Sheline et al. 1999), indicates that number of episodes is a factor which contributed to the reduction of whole brain corrected hippocampal volumes and suggests that depression itself may lead to altered brain structures.

Interestingly, overall we found high effect sizes in bipolar patients and a low effect or no effect in major depression. In context with these results we have to mention that the patients with BPD in the present study had significantly more affective illness episodes compared to the patients with MDD. However, beside the also noteworthy methodological differences to other studies there are some reports on smaller white or gray matter structures in BPD compared to MDD (Sassi et al. 2001; Coffman et al. 1990; Brambilla et al. 2004). In addition to that, Lopez-Larson et al. (2002) found that bipolar patients exhibited smaller gray matter volumes in the left superior and middle and right prefrontal subregions than healthy controls. In this study longer duration of affective illness was associated with smaller left inferior gray volumes. It remains open whether a subgroup of bipolar patients with distinct illness characteristics re-

garding number of episodes and severeness of psychopathology show increased volumes of subcortical brain regions. A recent meta-analysis of MRI brain morphometry studies in BPD (McDonald et al. 2004) demonstrates that strong heterogeneity exists for several subcortical regions. Probable sources of heterogeneity include methodological differences and clinical sample variation. These factors might affect morphology as measured by MRI.

Limitations of this study are given by the lack of data on drug exposure across the whole life-span since we could only collect data on psychotropic medication in the last three months prior to death. A recent study however could demonstrate drug effects on brain macrostructure even in such narrow time frames (Moore et al. 2000). Nevertheless effects of longer drug expositions remain unclear. The relative small sample size and thus probable under-powering of the current study are methodological problems which limit the conclusions that can be drawn from the reported findings. A further limitation is that several patients in both diagnostic groups were suicide victims and the possible impact of suicide on the obtained results should be considered. However, for a comparison the sample size for suicide victims within the monopolar and the bipolar group is quite small. For further studies case numbers should be increased.

In conclusion we found volume deficits of subcortical structures in affective illnesses with a focus on bipolar disorder, suggesting disrupted pathways involved in the regulation of mood. Surprisingly, whole brain volume did not differ between the groups. It is an open question whether distinct cortical areas or regional white matter compartments show increased volumes in patients with mood disorders.

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