Reduced Volume of Limbic System–Affiliated Basal Ganglia in Mood Disorders: Preliminary Data From a Postmortem Study

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Volumes of basal ganglia in postmortem brains of 8 patients with mood disorders and 8 control subjects without neuropsychiatric disorder were determined. Morphometry of serial whole-brain sections under the control of postmortem artifacts revealed reduced volumes of the left nucleus accumbens (–32%, P = 0.01), the right and left external pallidum (–20%, P = 0.04), and the right putamen (–15%, P = 0.04) in the patient group compared with the control group. These results suggest that, in particular, the limbic loop of the basal ganglia involving the nucleus accumbens and the pallidum is affected in mood disorders.

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In the last decade a considerable spectrum of structural abnormalities has emerged from neuroimaging studies in affective disorders.[1] Important findings have come from volumetric investigations of subcortical structures. Previous lesion studies showing an association of depressive syndromes with basal ganglia alterations[2–7] were confirmed by MRI measurements showing smaller volumes of the caudate and the putaminal complex in patients with unipolar depressive disorders[8,9] and larger caudate nuclei in male bipolar patients.[10] These data, as well as functional imaging studies demonstrating hypoperfusion,[11,12] hypometabolism,[13–15] or higher dopamine D_2 receptor occupancy in basal ganglia regions,[16,17] indicated that basal ganglia may play a crucial role in the pathology of affective disorders. Along with recognizing the complex architecture of basal ganglia circuits,[18] it appears to be important to know which anatomic elements of the basal ganglia are predominantly affected in mood disorders.

Surprisingly, there is a lack of postmortem studies of brain volumes in affective disorders. Investigations of postmortem brains offer the possibility to determine volumes of brain structures to a high degree of resolution. Thereby, complex nuclei like the basal ganglia can be measured in detail. Since regional volumetric brain alterations are an indicator of macropathology in cerebral diseases, distinct clusters of structural deviations

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that might be detected by postmortem morphometry could contribute to our knowledge of the brain biology of mood disorders. In the present study, a planimetric method is used to measure volumes in postmortem brains from patients with mood disorders as compared with control subjects. This procedure addresses the following question: Is there a focal macropathology in subcortical structures, especially in the basal ganglia, in patients with mood disorders? We report here the first results of our postmortem morphometric study.

METHODS

Subjects

Brains of 8 patients (3 males, 5 females, time of death between 1988 and 1991) with mood disorders according to DSM-III-R (major depression, $n = 4$; bipolar disorder, $n = 2$; schizoaffective disorder with mostly affective symptoms, $n = 2$) and of 8 sex- and age-matched control individuals (time of death between 1986 and 1990) without a history of neuropsychiatric disorder were investigated. Antemortem diagnoses were obtained by the careful study of clinical records and/or interviews of family members and physicians involved in treatment of the patients. By the same methods, neuropsychiatric disorders were also excluded in control individuals. Qualitative neuropathological changes due to neurodegenerative disorders (e.g, Alzheimer's, Parkinson's, or Pick's disease), tumors, and inflammatory, vascular, or traumatic processes were ruled out by an experienced neuropathologist. Individuals with abuse of alcohol or drugs were excluded by anamnesis, toxicology, and liver histology. Ages ranged from 39 to 62 years for patients and 38 to 65 years for control subjects. Mean age was similar in the two groups (patients, 47.75 ± 9.04 years; controls, 44.50 ± 0.58 years). Demographic and histological data including age, brain weight, postmortem delay, and tissue shrinkage factors are presented in Table 1. Clinical data are shown in Table 2.

Histological and Morphometric Procedures

Brains were removed within 4 to 72 hours after death. They were fixed in toto in 8% phosphate-buffered formaldehyde for at least 2 months (pH = 7.0, T = 15–20° C). Frontal and occipital poles were separated by frontal sections anterior to the genu and posterior to the splenium of the corpus callosum. The brainstem was isolated by a cut perpendicular to its longitudinal axis at the level of the oculomotor nerve. After embedding all parts of the brains in paraffin, serial coronal 20-µm-thick sections of the middle block were cut and mounted. Every 50th section was Nissl's (cresyl echt violet) and myelin stained (Heidenhain-Wölcke or Luxol fast blue). Thus, distance between the sections was 1 mm. Sampling of sections was performed systematically, using each stained section for investigation.

Volume shrinkage factors were determined for each brain by comparing areas of the most rostral and the most caudal section of each brain block before and after dehydration and embedding of tissue. Volume shrinkage factors were calculated by using the formula $VF = (A1/A2)^{3/2}$ where VF = volume shrinkage factor, A1 = cross-sectional area before processing of tissue, and A2 = cross-sectional area after processing of tissue.

Volumes of all telencephalic basal ganglia (putamen, caudate, nucleus accumbens, internal pallidum, external pallidum) were estimated from serial sections by a planimetric method described in detail previously.[19] For each brain, volumes derived by this method were multiplied by the individual brain tissue shrinkage factor in order to reach a calculation of structure volumes in the fresh brain.

The putamen, the head and the tail of the caudate, and the internal and external parts of the pallidum were clearly demarcated and were measured from their most rostral to the most caudal pole. Since the nucleus accumbens as the most ventral part of the striatum is difficult to distinguish from the caudate and the putamen by cytoarchitecture, we delineated this nucleus by drawing a line perpendicular to the internal capsule, with the use of the ventral corner of the lateral ventricle as a topographic marker point. As rostral border of the nucleus accumbens we defined the first section where the striatum was not completely separated by the internal capsule. As caudal border we took the most rostral slice where the anterior commissure was identified.

Planimetric measurements were performed by the first author (B.B.), blind to the diagnosis. To establish interrater and test-retest reliability, repeated measurements for 5 brains were carried out by two others (R.S., D.K.) for all investigated structures. Intraclass correlation analyses yielded highly corresponding results for the basal ganglia (r 0.95–0.99).

Data Analysis

Group comparisons of brain structure volumes were performed by analysis of variance (ANOVA) with fresh brain weight as covariate. Similarly, comparisons of the so-called Galaburda laterality index ($2 \times [\text{left} - \text{right}]/[\text{left} + \text{right}]$) were carried out to determine deviations in brain asymmetry.[20] The patients with unipolar depression ($n = 4$; mean age 48.0 ± 9.3 years) were selectively compared with an age- and sex-matched control group ($n = 5$; mean age 46.2 ± 13.2 years) by Student's two-tailed t-test. Similarly, patients with bipolar affec-

TABLE 1. Demographic and histological data of patients and control subjects

Patient/ Control No.	Sex/Age (yr)	Fresh Brain Weight (g)	Postmortem Delay (h)	Mean Volume Shrinkage Factor	Cause of Death
Patients					
1	M/47	1,670	24	2.22	Acute loss of blood in suicide by stabbing
2	F/39	1,400	48	2.28	Suicide by overdose of medication
3	F/46	1,410	48	2.33	Suicide by hanging
4	M/42	1,320	17	2.63	Suicide by hanging
5	F/62	1,300	72	2.22	Pulmonary embolism
6	M/39	1,520	14	1.73	Pulmonary embolism, myocardial infarction
7	F/61	1,240	70	1.89	Bronchopneumonia
8	F/46	1,300	4	2.16	Suicide by overdose of medication
Mean ± SD	48 ± 9	1,395 ± 141	37 ± 26	2.18 ± 0.3	
Control subjects					
1	M/47	1,450	24	2.74	Sudden cardiac death by myocardial infarction
2	F/48	1,170	48	2.16	Acute asthmatic state
3	M/38	1,550	19	2.22	Sudden cardiac death by myocardial infarction
4	F/50	1,055	72	2.00	Rupture of aortal aneurysm
5	F/65	1,100	24	1.83	Cardiac insufficiency, aortal stenosis, insufficiency of mitral valve
6	F/38	1,200	24	1.58	Pulmonary embolism
7	M/40	1,550	96	2.85	Myocardial infarction
8	F/30	1,500	48	2.22	Pulmonary embolism
Mean ± SD	45 ± 11	1,322 ± 211	44 ± 28	2.20 ± 0.4	

TABLE 2. Clinical characteristics of patients

Patient No./Sex/Age (yr)	Psychopathology	Yrs Ill	Psychotropic Medication in Last 4 Weeks	Psychiatric Diagnosis (DSM-III-R)
1/M/47	Melancholic type of major depression; at least one irritable manic episode; final depressive episode with agitation	9	None	Bipolar disorder (296.53)
2/F/39	Melancholic type of major depression with psychomotor retardation	NA	Amitryptiline 150 mg/d, diazepam 5 mg/d, lithium carbonate 900 mg/d	Major depression (296.23)
3/F/46	Melancholic type of major depression with hypochondriac delusion and psychomotor retardation	NA	Maprotiline 200 mg/d, haloperidol 5 mg/d	Major depression (296.24)
4/M/42	Predominantly irritable manic phases, mostly with delusions; depressive episodes of melancholic type with psychotic symptoms; final agitated schizodepressive episode with suicidal ideas	16	Lithium carbonate 900 mg/d, flunitrazepam 2 mg/d, amitryptiline 225 mg/d, chlorprothixen 150 mg/d	Schizoaffective disorder, bipolar type, mostly affective (295.70)
5/F/62	Schizodepressive episodes with melancholic type of major depression (predominantly anxiousness with alternating episodes of agitation and psychomotor retardation; last episode with agitated depressive syndrome)	11	Lorazepam 5 mg/d, flupentixol decanoate 20 mg/14d, haloperidol 20 mg/d	Schizoaffective disorder, depressive type, mostly affective (295.70)
6/M/39	Initial episode of major depression; later irritable manic syndrome followed by an agitated depressive episode	1.5	Haloperidol 15 mg/d (weeks 1–3), last week: 3 mg fluphenazine + 2 mg benperidol for 4 days; last 3 days no psychotropic medication	Bipolar disorder (296.42)
7/F/61	Melancholic type of major depression, predominantly with psychomotor retardation; last episode with delusions of guilt and sin, agitation	11	Amitriptyline 90 mg/d, haloperidol 5 mg/d, nitrazepam 2,5 mg/d except for last 4 days	Major depression (296.34)
8/F/46	Melancholic type of major depression, several episodes with psychomotor retardation and delusions of guilt and sin	13	Amitriptyline 200 mg/d, haloperidol 15 mg/d, diazepam 5 mg/d, lithium carbonate 900mg/d	Major depression (296.34)

Note: NA = not available.

tive or schizoaffective disorder ($n=4$; mean age 47.5 ± 10.2 years) were compared with an age- and sex-matched control group ($n=4$; mean age 47.5 ± 12.3 years). Two-tailed *t*-tests were also used for group comparisons with respect to age, postmortem delay, and brain weight. Generally, a *P*-value of 0.05 was considered to be significant.

Pearson linear correlations were used to examine effects of several clinical and neuropathological parameters (e.g., age, duration of illness, postmortem delay, brain weight, medication) on brain structure volumes.

Correlations of volumetric measures with antidepressant and neuroleptic medication were calculated by using mean daily doses given in the last 4 weeks of life (see Table 2). Mean daily medication doses over the last 3 months were comparable to those of the last 4 weeks. Using Student's *t*-test, volumes of all investigated structures were compared between patients who had received sedatives or lithium over the last 4 weeks and those who were not treated by these drugs. Statistical applications were performed by using the software package SPSS 6.13.

RESULTS

Group Comparisons

Results of comparisons of all patients taken together ($n=8$) versus control subjects ($n=8$) are shown in Figures 1 and 2. The following basal ganglia showed significantly smaller volumes in patients compared with controls: 32% smaller left nucleus accumbens ($P=0.01$); 20% smaller left and right external pallidum ($P=0,02$); and 15% smaller right putamen ($P=0.04$). The four unipolar depressed patients also had smaller volumes of the left nucleus accumbens when compared with age- and sex-matched control subjects ($P=0.048$). When patients with bipolar or schizoaffective disorder together ($n=4$) were compared with age- and sex-matched controls ($n=4$), the left nucleus accumbens also evidenced a trend to smaller size ($P=0.075$). None of the investigated volumes differed between the bipolar/schizoaffective and the unipolar groups (all $P>0.24$).

Group comparisons of Galaburda laterality index showed no difference in any investigated structure with respect to laterality ($P>0.24$).

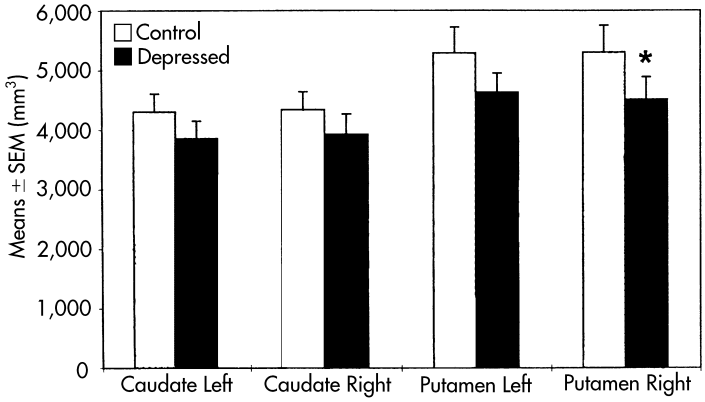
Effects of Clinical and Neurohistological Parameters on Structure Volumes

Age, brain weight, and postmortem delay did not differ between patients and controls ($P=0.52$, $P=0.43$, $P=0.60$, respectively). Moreover, structure volumes expressed as a function of brain weight did not correlate with age (all *r* between –0.46 and 0.03; all $P>0.06$) or postmortem delay (all *r* between –0.02 and 0.44; all $P>0.08$).

Because all patients treated with antidepressants received tricyclic or tetracyclic antidepressants, daily medication doses were comparable. There was no correlation between any of the investigated volumes and mean daily doses of antidepressants (all *r* between 0.23 and 0.64; all $P>0.08$) or neuroleptics in chlorpromazine equivalents (all *r* between –0.13 and –0.63; all $P>0.09$). Volumes of patients treated with benzodiazepines ($n=5$) did not differ from volumes of those who had not received benzodiazepines ($n=3$; all $P>0.11$). Moreover, no differences between volumes were seen when patients treated with lithium ($n=3$) were compared with those who had not received lithium ($n=5$; all $P>0.08$).

No correlation was found between duration of the illness and any of the investigated volumes (all *r* between 0.31 and 0.80; all $P>0.05$).

FIGURE 1. Brain structure volumes of patients with affective disorder ($n=8$) and control subjects ($n=8$): caudate and putamen. *Significant *P*-value.



DISCUSSION

Results of the present postmortem study confirm and specify findings of basal ganglia abnormalities reported from CT or MRI studies. Neuroimaging studies have shown that structural abnormalities exist in basal ganglia of patients with mood disorders. In nonelderly patients with unipolar depression, controlled MRI studies found at least a trend for reduced volumes of the caudate and the putaminal complex.[8,9,21] However, this seems not to be the case for bipolar disorder.[10,21–23]

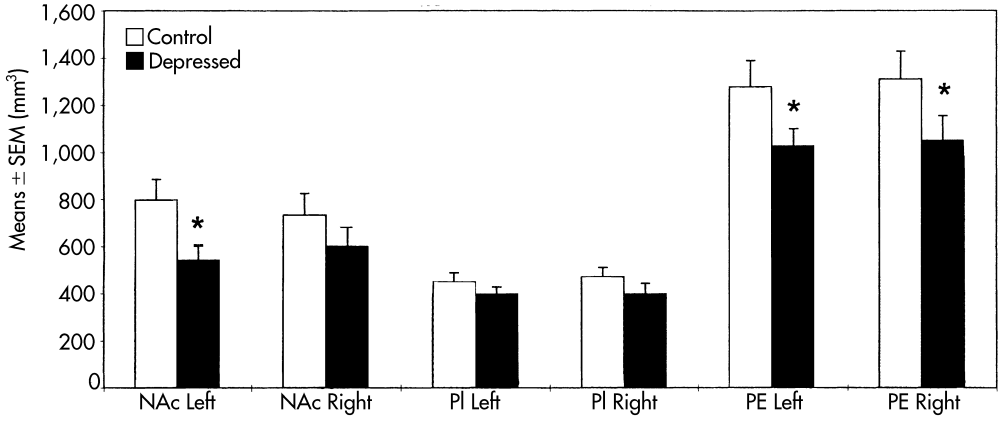
In contrast to neuroimaging technology, postmortem morphometry provides the option of delineating and separating even small brain nuclei, such as the nucleus accumbens or the internal and external part of the pallidum, that have different connections and functions in basal ganglia circuits. These differences might explain in part the inconsistent results of MRI studies in which larger complexes of the basal ganglia were measured, such as the lentiform nucleus consisting of the pallidum and the putamen. More subtle structural abnormalities still cannot be detected by MRI. In the basal ganglia we found a focally accentuated volume reduction of the left nucleus accumbens, the external pallidum bilaterally, and the right putamen. Volumes of the left nucleus accumbens were significantly smaller in unipolar depressive patients and tended to be reduced in bipolar or schizoaffective patients.

This finding may have pathophysiological relevance, since the nucleus accumbens is part of the ventral striatum and thereby belongs to the limbic nuclei.[18,24,25] There is a reciprocal projection between the nucleus accumbens and the ventral pallidum,[26,27] which share common neuromodulators such as γ-aminobutyric acid and opioids.[28,29] Furthermore, the nucleus accumbens is the terminal of the mesolimbic dopaminergic projection from the ventral tegmental area.[30,31] These two pathways are known to be relevant to rewarding effects[32–34] and locomotion.[35–38] Moreover, there exist afferents to the nucleus accumbens from cortical and subcortical limbic structures such as the entorhinal cortex, prelimbic and infralimbic cortices, the anterior cingulate, the hippocampus, the mesencephalon including the dorsal raphe nucleus, the basal amygdala, and the lateral hypothalamus.[39–41] For this reason the nucleus accumbens is believed to be a pivotal structure at the interface of the limbic system and the basal ganglia and might be associated with psychic functions like mood and motivation.[42] The volume reduction of the left nucleus accumbens suggests pathology in the limbic loop of the basal ganglia at a site where information from neocortical inputs is modulated by limbic afferents before entering the nucleus accumbens. From the accumbens, information is transferred to the pallidum as one of the outputs of the basal ganglia to the thalamus, the cortex, and the brainstem.[18,43] The question remains open whether distinct compartments of the accumbens (that is, the core or the shell),[44] and thereby specific afferents to this nucleus, are altered in mood disorders.

Long-term application of neuroleptics reportedly may cause neuronal hypertrophy in the rat striatum[45] and volume increases of the striatum in humans.[46,47] These results are consistent with findings of a hypertrophic striatum in patients with Parkinson's disease, apparently a result of dopaminergic underactivity.[48] Thus, neuroleptic medication taken by 6 of 8 patients in our study might have increased volumes of the caudate and the putamen, which possibly were reduced in an unmedicated state.

Moreover, it is conceivable that only a distinct ana-

FIGURE 2. Brain structure volumes of patients with affective disorder ($n = 8$) and control subjects ($n = 8$): nucleus accumbens and pallidum. NAc = nucleus accumbens; PI = internal pallidum; PE = external pallidum. *Significant *P*-value.



tomic compartment of the striatum, such as the striosomes or the matrix, will show structural abnormality. This distinction might prove relevant, since connectivity with the neostriatum is topographically organized in these compartments; for example, most projections to the pallidum originate from the matrix,[49] and inputs from limbic system–affiliated structures are largely directed to striosomes.[50] Postmortem studies using acetylcholine-esterase staining might be useful to address the question of whether structural abnormalities in the anatomical and functional parcellation of the striatum exist in affective disorders.

Several neuroanatomical models of mood regulation have been proposed in recent years.[1,51–57] From these models it could be hypothesized that the striatum and the ventral pallidum might be key structures of the basal ganglia implicated in the pathology of depressive disorders. Results of our study confirm this assumption, particularly emphasizing the role of ventral parts—that is, the limbic parts of the striatum—in this pathology. The structural abnormality of limbic basal ganglia in patients with affective disorders is consistent with the notion that these subcortical structures might be involved not only in the control of movement, but also in the motivation for action[58] and psychomotor behavior.[59] Both lack of drive and psychomotor retardation represent foci of psychopathology in mood disorders.

A question that has to be addressed is whether volume alterations could be caused by medication. Patients included in this study received variable amounts of antidepressants, neuroleptics, sedatives, and lithium. Although antidepressants may be toxic in hepatocytes,[60] there is no evidence, at least from clinical data, that antidepressants cause shrinkage of brain tissue.[61] From animal work, antidepressants are shown to 1) counteract cell death caused by neurotoxins,[62] 2) attenuate stress-induced morphological changes in the rat hippocampus,[63] and 3) elicit regenerative changes in the cerebral cortex after toxic lesions.[64] In our study, mean daily doses of tricyclic and tetracyclic antidepressants given in the last 4 weeks of life did not correlate with any of the structure volumes. Thus, it appears unlikely that antidepressant medication might be responsible for the volume alterations found in this study.

Furthermore, mean daily doses of neuroleptics did not correlate with any of the significantly changed volumes. As noted above, however, chronic application of neuroleptics can elicit volume increase of parts of the striatum. Thus, the finding of smaller volumes of the nucleus accumbens does not seem to be a result of neuroleptic medication. On the other hand, although neuroleptic medication in most cases in this study group was at modest levels, it could not be ruled out that hypertrophy induced by neuroleptics might have covered primarily existing volume deficits of the putamen and the caudate in patients. Besides differences in measurement strategies, the divergent amounts of neuroleptic medication might in part explain the discrepant results between our study and MRI studies that described smaller volumes of caudate and putamen in unipolar depressive patients or a greater caudate nucleus volume in bipolar disorder.[8–10]

In addition, comparisons of patients who received either sedatives or lithium with those who got no such medications yielded no differences with respect to volumes of the investigated structures. Moreover, illness duration did not correlate with any of the structure volumes. It is therefore unlikely that smaller volumes of the left accumbens, the right putamen, and the lateral pallidum bilaterally are a result of medication.

A crucial point in the evaluation of postmortem volumetry is to consider perimortal and postmortal processes that may influence brain structure. Protracted agonal states can induce acute alterations of brain tissue due to hypoxia. In our study, 2 patients (cases 6 and 7) and 2 control subjects (cases 5 and 7) suffered 3 or 4 days of agony. By neuropathological examination, none of these brains showed macroscopically visible edema. Acute nerve cell alterations or phagocytosis were not present in the measured structures. Moreover, possible alterations due to agonal state are comparable in patients and control subjects.

Postmortal processes such as postmortem delay and shrinkage of tissue due to embedding in paraffin were not different in the patients and the control subjects. Shrinkage factors were included in the volume calculations. Mode of tissue fixation did not influence our morphometric data, since alteration of brain weight by fixation with 8% formaldehyde is remarkable only in the first 4 weeks of fixation.[65–67] The structural abnormalities found in the patient group are not an effect of general reduced brain size, since brain weight of the investigated patients was even slightly higher than that of control subjects and brain weight was calculated as a covariate.

Although the volume reduction of the left nucleus accumbens was most prominent in unipolar depressed patients, it remains unclear whether our findings are specific to certain subtypes of mood disorders, since the sample of patients was too small. Moreover, the limited number of cases here reported emphasizes the pilot character of the study.

In sum, results of this preliminary report support the hypothesis that predominantly limbic parts of the basal ganglia—that is, the nucleus accumbens and the pallidum—are a focus in the pathomorphology of affective

disorders. Because of limitations in neuroimaging technology, such subtle structural deficits of basal ganglia have not yet been shown in affective disorders. The histological basis underlying the described volume alterations, their etiology, and their relationship to depressive symptomatology remain to be clarified. Larger samples are needed in order to detect possible structural differences of basal ganglia between unipolar depression and bipolar or schizoaffective disorder.

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