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The Crucial Role of Frontostriatal Circuits for Depressive Disorders in the Postacute Stage After Stroke

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Objective: This study analyzes lesion configuration in patients in the post-acute stage after first single unilateral stroke who suffered from depressive disorders. **Background:** Recent studies indicate a biological origin of poststroke depressive disorders. Due to differences in times of investigation, methods applied, and patient selection, most data are not comparable. Furthermore, only a few studies of poststroke depression report detailed neuropsychologic assessments. **Methods:** We investigated 20 consecutive patients who were diagnosed as depressive according to DSM-III-R criteria and exhibited no other severe illness, had no history of neurologic or psychiatric disease, and who were either not aphasic, or only mildly aphasic. A structured clinical interview, self-based and observer-based depression rating scales, a comprehensive neuropsychologic and neurologic examination and ADL-measurement were applied. Neuroradiologic analysis was based on standardized computed tomography scans. **Results:** Nine of 10 subjects with left hemisphere strokes exhibited a major depression and 7 of 10 subjects with right hemisphere infarcts a minor depression. The most prominent neuropsychologic deficits were found in frontal lobe associated tasks. Type and severity of depression were not related to the severity of neurologic symptoms or impairment in activities of daily living. For both major and minor depression the maximal overlap of lesions was found in subcortical areas, including parts of the caudate nucleus, posterior parts of the putamen, and the deep white matter. **Conclusions:** The findings support the theory that poststroke depression is related to the dysfunction of (cortico-) striato-pallido-thalamic-cortical projections that modulate cortico-thalamo-cortical loop systems. **(NNBN 1999;12:236–246)**

Poststroke depression is a frequent problem in stroke rehabilitation and has a negative impact on patients' recovery (1,2). Considerable variability in published prevalence rates exists (3,4), depending on different assessment strategies and methods as well as on different criteria for patient recruitment. Longitudinal prospective studies show that the prevalence as well as the type and the severity of depression may change during the course of illness (5–7), indicating differences in the etiopathogenesis of poststroke depressive disorders. Apart from the clinical importance of adequate diagnosis and treatment (8), the analysis of neuropsychologic and neuroanatomic correlates of poststroke depression may provide valuable insight into the pathophysiology of depressive disorders. A substantial number of studies that examined the association between lesion location and depression reported a significantly higher prevalence and severity of depression in patients with left hemisphere stroke (5–7,9–12) and a negative correlation between depression severity and the proximity of the lesion to the left frontal pole. Although some other investigations of poststroke depression were not able to replicate these findings (2,13–16), the specific association of depression and lesion location gave a first indication for the biological origin of poststroke mood alterations. Further evidence for the biological explanation of poststroke depression came from studies which demonstrated local decrease of cerebral blood flow (17,18), alterations of cortical receptor sensitivity (19,20), or

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changes in neurotransmitter metabolite concentrations in cerebrospinal fluid (21). In previous studies, based on consecutive samples of stroke patients (22,23), our group demonstrated that major depressive disorders after stroke are associated with left basal ganglia lesions. The present study aimed at the investigation of neuroanatomic and neuropsychologic correlates of depression in a carefully and strictly selected sample of depressed patients in the postacute stage of stroke.

PATIENTS AND METHODS

Patients

During a 2-year period of investigation we studied patients who fulfilled the following selection criteria:

- first completed stroke within the previous 4 months;
- presence of a single unilateral demarcated lesion in computed tomography imaging;
- no concomitant severe organic illness;
- no history of neurologic disorder with central nervous system involvement, psychiatric disorder, or alcohol or drug abuse;
- no severe aphasic disorder that could prevent a structured clinical interview and a standardized neuropsychologic examination.

Two acute care clinics of neurology and two centers of neurologic rehabilitation participated at the study. All stroke patients were screened according to the selection criteria described above. Patients who fulfilled all criteria were examined for depressive disorders by the use of different rating scales and a structured clinical interview. Only subjects who exhibited depressive disorder classified as major depression or dysthymic disorder/"minor depression" according to DSM III-R criteria were included in the study. Informed and written consent was obtained by all patients.

METHODS

All patients were assessed with a detailed neurologic examination based on different stroke scales with a grading of the severity of neurologic symptoms. Furthermore, the following neuropsychiatric, neuropsychologic, and neuroradiologic assessments were applied:

Neuropsychiatric Investigations

All subjects were assessed with the following instruments:

1) Structured Clinical Interview for DSM-III-R (SCID (24), German version (25,26); The SCID is a semi-structured diagnostic interview used to assess major Axis I DSM-III-R disorders. As in most other studies in this field, we ignored the 2-year duration criterion of the DSM to diagnose a dysthymic depression. Therefore, we use the term *minor depression*, which indicates that the subjects presented all symptoms of a dysthymic disorder with a duration less than 2 years.

For additional information on the severity of depression, one self-rating and two observer-rating scales were applied:

2) Beck Depression Inventory (BDI) (27)

3) Cornell Depression Scale (CDS) (28,29)

4) Montgomery-Åsberg Depression Rating Scale (MADRS) (30)

Neuropsychologic Assessment

The following tests and assessment procedures were used to quantify neuropsychologic deficits:

Memory/Learning

- Auditory-Verbal-Learning-Test
- Wechsler Memory Scale-Revised: subtests Visual Paired Associates and Digit Spans forward and backward
- Corsi-Block-Tapping Test (forward and backward)

Verbal and Nonverbal Fluency

- Five-point Test (31)
- Controlled Oral Word Association (lexical [*s*-words] and semantic [animal names] fluency)

Visuo-constructive Performance

- Block design

Attentional Performance

We applied the following subtests of the computerized "Test for Attentional Performance" (32):

- Alertness (phasic and tonic alertness, simple reaction times)
- Go/Nogo (response selection/inhibition)
- Flexibility (motor and cognitive/attentional shift)

Aphasia Screening

All patients were screened for aphasia. In case of aphasic symptoms the Aachen Aphasia Test (33) was carried out by a speech pathologist. Patients with moderate or severe speech comprehension deficits were excluded from the study.

Impairments in activities of daily living were assessed with an extended version of the Barthel index (34).

Neuroradiologic Investigations

Only computed tomography scans are considered in the present investigation. The scans were performed in standardized slices without contrast enhancement and were required to show a demarcated lesion but no pre-existing pathology. As described by Blunk et al (35) and by Poeck et al (36), site and extent of lesion was measured in the computed tomography films and then transposed onto a set of nine standardized grids. These grids were analyzed by software developed in our laboratory that computes lesion volumes (based on a counting of voxels and expressed as a percentage of forebrain volume) and produces superimposition diagrams. Lesions were analyzed with respect to lesion topography (based on Damasio and Damasio (37) and Matsui and Hirano (38)) and to territories of vascular supply (according to Damasio and Damasio (37)), including the territories of the deep perforators of the carotid system of Ghika et al (39). According to the definitions of Robinson et al (9), the lesions were classified as anterior and posterior and the average distance from the frontal pole in percent of overall anterior-posterior distance was calculated.

Statistical Analysis

Due to small sample size and ordinal-scaled data, statistical analysis was performed with nonparametric procedures (χ^2-Fisher's exact tests, Mann-Whitney U-tests, Spearman rank correlation coefficients). All levels of significance reported in the result section are two-tailed.

RESULTS

During a 2-year period of investigation, only 20 patients fulfilled all the selection criteria described in the previous section. Table 1 shows sociodemographic, neuropsychiatric, and neuroradiologic data for all patients. Ten subjects had left hemisphere infarctions, and 10 subjects suffered from right hemisphere infarctions. Both groups were comparable with respect to age, years of education, and familial or professional status. Distribution of sex, however, differed between groups with more women in the left hemisphere stroke group, and more men in the right hemisphere stroke group (two-tailed Fisher's exact test: $p = 0.069$). All subjects were investigated within the first 4 months after stroke.

Only patients with major depressive disorders received antidepressive drug treatment. Four patients with a left hemisphere stroke were treated with tricyclic antidepressants ($n = 3$) or a monoamine oxydase inhibitor ($n = 1$) and one patient with a right hemisphere stroke received a selective serotonin reuptake inhibitor. Drug treatment was started after diagnosis of depression and neuropsychiatric and neuropsychologic investigations were performed within the same week. No patient reported side effects of antidepressants at the time of neuropsychologic assessment and no patient was treated with minor or major tranquillizers or any other drug which could induce depression

TABLE 1. *Sociodemographic, neuropsychiatric and neuroradiologic data of patients with left and right hemisphere lesions*

	LHS	RHS	p*
Number of patients	10	10	
Age, median (range)	62.5 (35–78)	62.5 (33–69)	ns
Handedness (right/left/ambidextrous)	8/1/1	7/3	ns
Sex (female/male)/(*n*)	7/3	2/8	0.07
Formal education (*n*)			
<5 years	1	0	ns
5–9 years	0	8	
10–12 years	9	1	ns
>13 years	0	1	ns
Time of investigation, weeks following CVA, median (range)	4 (2–14)	7 (2–17)	ns
Onset of depression, weeks following CVA, median (range)	0 (0–7)	0 (0–13)	ns
Depression			
Major/Minor Depression (*n*)	9/1	3/7	0.02
BDI-Scores, median (range)	16.5 (9–28)	11 (5–23)	ns
CDS-Scores, median (range)	14 (5–18)	9 (6–18)	ns
MADRS-Scores, median (range)	13.5 (9–23)	15 (8–22)	ns
Antidepressive drug treatment, *n*(%)	4 (40)	1 (10)	ns
Lesion location (*n*)			
Frontal lobe	4	7	ns
Parietal lobe	4	6	ns
Temporal lobe	4	9	ns
Occipital lobe	0	0	ns
Insular cortex	3	10	0.003
Caudate nucleus	5	7	ns
Putamen	7	9	ns
Pallidum	6	7	ns
Thalamus	0	0	ns
Vascular supply (*N*)			
Anterior cerebral artery	0	0	ns
Middle cerebral artery	10	10	ns
Anterior choroideal artery	7	9	ns
Lenticulostriate arteries	7	7	ns
Posterior cerebral artery	0	0	ns
Volume of lesion, median (range)	78 (.27–3.75)	2.5 (.13–19.9)	0.04
Anterior lesions (*n*)	4	3	ns
Posterior lesions (*n*)	2	0	ns
Nonclassifiable (*n*)	4	7	ns
ANTPER, median (range)	37.5 (21–56)	30 (18–48)	ns

*Two-tailed p values according to U (exact) or X^2 (Fisher's exact) tests.

ANTPER, average distance of the lesion from the frontal pole; BDI, Beck Depression Inventory; CDS, Cornell Depression Scale; CVA, cerebrovascular accident; LHS, left hemisphere stroke; MADRS, Montgomery-Åsberg Depression Rating Scale; ns, not significant; RHS, right hemisphere stroke.

or affect the cognitive state by means of central nervous side effects.

Neuropsychiatric Examinations

Although all subjects fulfilled DSM-III-R criteria of major or minor depression ("dysthymic disorder") there was a wide range of depression severity (see Table 1). We found significant correlations between observer rating scales (rCDS-MADRS = 0.58, p = 0.007) and between CDS and BDI (r = 0.53, p = 0.017), but no significant correlation between MADRS and BDI (rMADRS-BDI = 0.28, p = 0.224). Twelve subjects (nine with left and three with right hemisphere lesions) showed a major depressive disorder and eight patients exhibited a minor depression (one with left and seven with right hemisphere lesions). Major depression was significantly more frequently associated with left hemisphere lesions (p = 0.019, Fisher's exact test). Patients with major depressive disorders presented significantly higher depression severity ratings both in the BDI (U = 8, p = 0.001) and the CDS (U = 11, p = 0.003). Major depression was associated with more severe mood-related signs of depression (anxiety, sadness, lack of reactivity, irritability), behavioral disturbances (retardation, loss of interest), physical signs (appetite and weight loss, lack of energy), sleeping disorders (multiple awakenings during sleep and early morning awakening), and more severe self-depreciation and pessimism. Statistical significance, however, was reached only for loss of appetite (p = 0.001). Figure 1 shows the profile of symptoms of depression in major and minor depressive stroke patients according to the different sections of the CDS. Subjects with major depression presented more mood related (p = 0.069) and physical signs (p = 0.047) of depression as well as more frequent disturbances of cyclic functions (p = 0.069).

Neuropsychologic and Neurologic Assessment

According to the Aachen Aphasia Test criteria, four patients with left hemisphere lesions exhibited mild to moderate fluent aphasia (two Wernicke and two anomic aphasia, respectively), and four patients showed some residual aphasic symptoms which were not classifiable on the basis of the Aachen Aphasia Test. In all aphasic subjects, however, sufficient speech comprehension and production ability to complete a structured clinical interview and the Beck Depression inventory could be secured. We found differences in the neuropsychologic performance between patients with left and right hemisphere stroke mainly in tasks which rely on verbal abilities (verbal fluency and verbal memory; see Table 2). Except for the nonverbal learning task, no significant differences between groups could be calculated in all other domains of

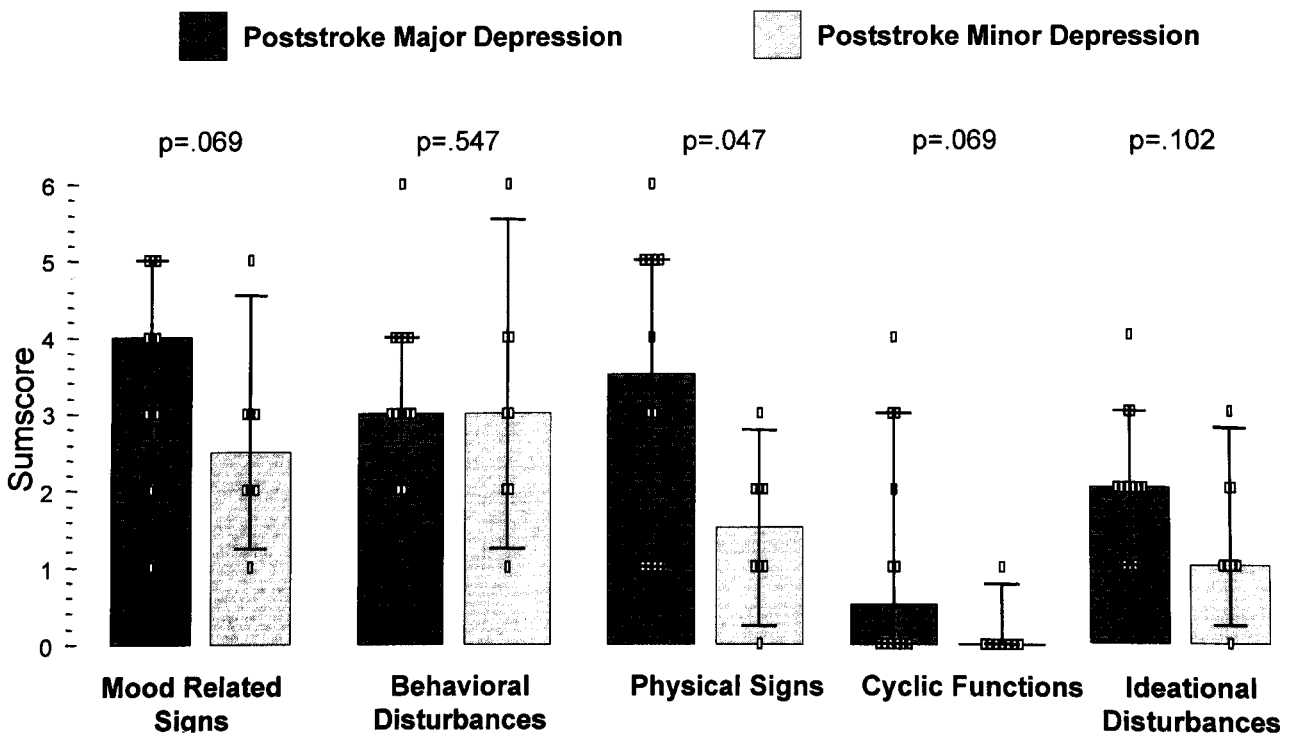

FIG. 1. Profile of depressive symptoms in strike patients with major and minor depression corresponding to the different sections of the Cornell Depression Scale.
Bars represent median ± 95% confidence interval, p values according to exact U-test.

TABLE 2. *Results of neuropsychologic tests*

	LHS	z*	RHS	z*	p†
Auditory-verbal-learning-test score, median (range)	26 (12–40)	−3.2	42.5 (16–62)	−1.0	$p = 0.008$
Visual paired associates	3 (1–16)	−2.4	8 (5–18)	−1.1	$p = 0.015$
Digit span forward	6 (2–8)	−1.5	5 (2–8)	−2.2	ns
Digit span backward	3 (0–6)	−1.6	3.5 (0–7)	−1.3	ns
Corsi-block-tapping forward	4 (1–7)	−1.2	4.5 (0–7)	−0.9	ns
Corsi-block-tapping backward	4.5 (2–7)	−1.6	6 (2–8)	−0.6	ns
Five-point test	13.5 (4–40)	−1.9	20.5 (9–31)	−1.1	ns
Category fluency	9.5 (2–23)	−3.8	26 (0–51)	−2.0	$p = 0.008$
Letter fluency	3.5 (0–18)	−2.8	20.5 (1–31)	−0.6	$p = 0.017$
Block design	16.5 (6–29)	−1.2	12 (0–32)	−1.7	ns
Alertness, msec, median (range)	310.5 (214–458)	−1.4	301 (233–577)	−1.2	ns
Go/nogo, msec, median (range)	512 (401–758)	−0.6	497 (403–776)	−0.5	ns
Flexibility, msec, median (range)	2461 (1183–3577)	−5.2	1940 (955–2787)	−3.4	ns
Visual hemineglect (*n*)	2		4		ns
Aphasia (*n*)	8		0		$p < 0.001$
Extended Barthel index, median (range)	117.5 (75–190)		115 (75–200)		ns

*z-Scores compared to the performance of 20 age-matched and sex-matched healthy control subjects.
†Two-tailed *p* values according to U- (exact) or χ^2 (Fisher's exact)-tests.

neuropsychologic performance. Table 2 also presents z-scores calculated on the neuropsychologic test performance of 20 age-matched and sex-matched healthy control subjects. The distribution of z-scores indicates that, apart from speech dependent tasks, the most prominent neuropsychologic deficits were found in frontal lobe-associated tasks: working memory, fluency, flexibility, and error control (not documented in Table 2). With respect to both type and severity of neurologic symptoms (motor or sensory disturbances, cranial nerve disorders, etc.) subjects with right or left-hemisphere strokes did not differ significantly. Impairment in activities of daily living (extended Barthel index) was comparable in both groups ($U = 46$, $p = 0.762$).

Neuroradiological Examinations

Lesion locations in all patients are shown in Figure 2 (lesion configurations as marked in the templates correspond to the upper cut of the slices). The group of patients with left hemisphere stroke exclusively presented subcortical infarctions, whereas the cortex was involved in the majority of patients with right hemisphere lesions. Except for a significantly more frequent involvement of the insular cortex in right hemisphere infarctions ($p = 0.003$), we found no significant differences between groups with respect to lesion location, lesion classification, and anatomy of vascular supply of infarcted areas (see Table 1). All patients showed lesions in the internal carotid artery territory of vascular supply, which includes most of the basal ganglia. The thalamus seemed to be spared in all subjects. To some extent, these hemisphere differences in lesion configuration reflect exclusion criteria that were biased against large left hemisphere strokes leading to moderate or severe aphasia. Accordingly, patients with right hemisphere strokes had significantly higher volumes of lesion ($U = 23$, $p = 0.043$). The majority of lesions were not classifiable as anterior or posterior according to the definition of Robinson et al (9), and no significant difference of the average distance of the lesion from the frontal pole was found.

Associations Between Neuropsychologic and Neurologic Impairment and Type and Severity of Depression

Significant correlations between depression severity and deficits in neuropsychologic performance were mainly found between frontal lobe-associated tasks and the patients' self rating of depression severity. Subjects with higher BDI scores performed significantly worse in a working memory task (block tapping backward—BDI: $r = -0.47$, $p = 0.035$) and in a verbal fluency (semantic fluency—BDI: $r = -0.59$, $p = 0.007$) and verbal memory task (auditory verbal learning—BDI: $r = -0.61$, $p = 0.004$). The correlation between both verbal tasks and BDI scores remained significant when we controlled for aphasic disorders. Depression severity as measured with self-based (BDI) or observer-based rating scales (CDS, MADRS) was not significantly correlated with the degree of impairment in activities of daily living (extended Barthel index). Furthermore, the degree of subjective complaints of depressive symptoms was not correlated with neuropsychologic measurements (e.g., retardation, concentration disorders or loss of energy and attentional performance, speed of information processing).

Associations Between Neuroradiologic Data and Type and Severity of Depression

Subjects with left-hemisphere lesions exhibited major depressive disorders significantly more frequently (two-

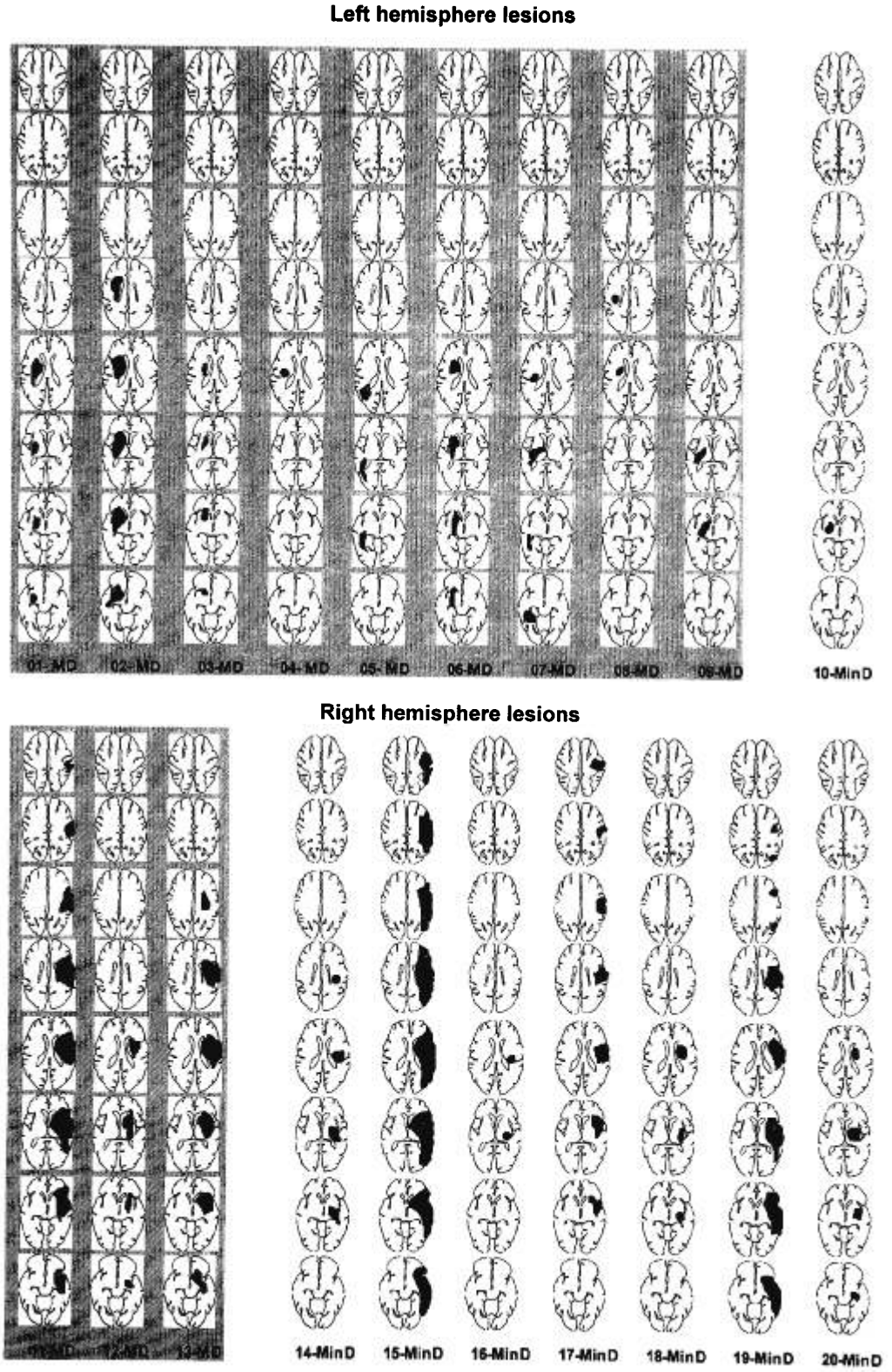

FIG. 2. Lesion location in depressive patients with left and right hemisphere lesions.

tailed Fisher's exact test: $p = 0.019$). Anterior lesions were not associated with more severe depressive disorders as measured in both observer rating scales and the Beck depression inventory. Furthermore, we found no significant correlation between measurements of depression severity and the proximity of the lesion to the frontal pole in either the two subgroups or in the whole sample of depressive patients. Figure 3 presents diagrams of lesion superimpositions in subjects with major and minor depression. In both groups the maximal overlap of lesions was found in subcortical areas. In subjects with major depression, maximal overlap of infarcted brain areas was observed in the left hemisphere periventricular part of the corpus nuclei caudati and subcortical white matter ($n = 5$ subjects) and the posterior part of the putamen ($n = 4$ subjects). Maximal overlap of infarcted areas in patients with minor depression was found in the right hemisphere periventricular white matter ($n = 4$ subjects) and the posterior right pallidum ($n = 4$ subjects).

DISCUSSION

In this study we analyzed the association of depressive disorders in the postacute stage after stroke with pathoanatomic, neuropsychologic and clinical-neurologic data. Because we excluded all patients who had a history of psychiatric or neurologic disorder or showed previous pathology or bilateral or multiple lesions in computed tomography scans, our study group was a highly selected and small sample of patients taken from a large population. During a 2-year period of investigation, 80 percent of all patients initially enrolled in the study with clinical signs of depression after stroke had to be excluded because they did not meet all selection criteria. Therefore, our data do not allow any conclusions on the incidence of depressive disorders after stroke. On the other hand, we carefully controlled premorbid and postmorbid variables which may influence or cause depressive disorders after stroke.

The study produced three major findings. First, major depression was found significantly more frequently in patients with left hemisphere lesions, whereas minor depressive symptoms were predominantly found in patients with right hemisphere infarctions. Second, type and severity of depression after stroke are not associated with neurologic impairment or reduced activities in daily living. Third, basal ganglia lesions seem to play a crucial role in the pathophysiology of depressive disorders after stroke. In the postacute stage after first single and unilateral stroke, patients with first left hemisphere lesions exhibited significantly more frequent major depressive disorders than patients with right hemisphere lesions. Our findings confirm a series of previous publications which demonstrate that poststroke depression after left hemisphere infarction is etiologically and phenomenologically distinguishable from right hemisphere depression (40) and tends to take a different clinical course (5,41). Evidence for distinct depressive syndromes after left and right hemisphere strokes also came from studies that demonstrated a higher genetic vulnerability only in patients with right hemisphere poststroke depression (42,43). In this study, however, we were not able to prove this hypothesis because a psychiatric history was an exclusion criterion.

Several authors reported a positive relation between severity of poststroke depression and the degree of physical impairment (2,14,44). In this study we found neither an association between number and severity of neurologic symptoms and severity of depression, nor a significant correlation between impairment in activities of daily living and the degree of depressive alteration. With respect to the postacute stage after stroke our data do not support the hypothesis that depression simply reflects a psychological reaction to the illness. In contrast to the psychological explanation of poststroke depression our results demonstrate that lesion location plays a crucial role in the pathogenesis of poststroke depressive disorders. In 16 of our 20 patients with poststroke depression, the involvement of basal ganglia structures in the infarcted brain area could be secured. Superimposition analysis revealed a maximal overlap of lesions in the caudate nucleus and the posterior parts of the putamen and pallidum. These findings replicate the results of previous studies by us (22,23) and by other groups (10,11,45–47). In contrast to other studies of the Robinson/Starkstein group (9,10,48), we found no significant associations between classification of lesion or proximity of the lesion to the frontal pole and type or severity of depression. This finding, however, might be influenced by the exclusion of nondepressive stroke patients as well as depressive patients with medium-severe to severe nonfluent aphasia and anterior lesions. Furthermore, we found no correlation between the volume of brain infarction and the severity of depression. If basal ganglia lesions, however, play an important role in the pathogenesis of poststroke depressive disorders, dichotomies of anterior or posterior lesion location must fail to demonstrate specific subcortical regions of interest. Although not all patients in our study group showed basal ganglia lesions, the data indicate a prominent role of basal ganglia in the pathophysiology of poststroke depressive disorders. Our findings support theories on limbic-striatal-pallidal-thalamo-(prefrontal) cortical circuits involved in the functional neuroanatomy of unipolar depressive disorders. Although at present there is no conclusive theory on the complex interaction of different neurobiochemical pathways involved in the pathophysiology of depression (49), various conceptualizations of the functional neuroanatomy of mood disorders converge on basal ganglia-thalamo-cortical circuits (50–53). Most of these theories

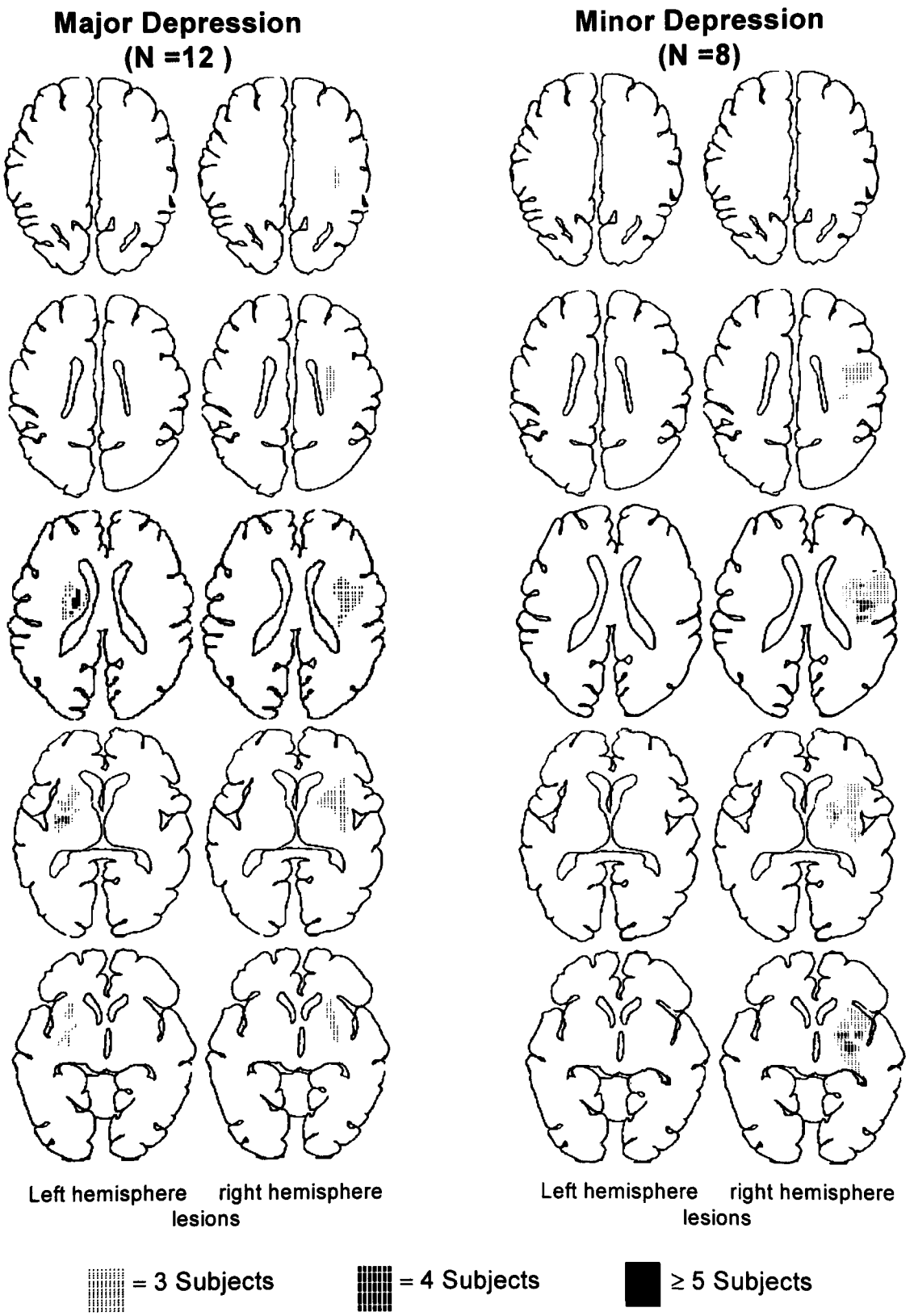

FIG. 3. Superimpositions of lesions in patients with major and minor depression.

suggest that abnormal reverberatory activity in thalamocortical circuits induced by decreased or lesioned inhibitory striato-pallidal control may be the neuronal substrate of fixed emotional and cognitive sets in depressive disorders. Our results, as well as the findings of previous studies (22,23), strongly support this hypothesis and we have shown elsewhere that basal ganglia lesions in poststroke depressive disorder can be interpreted in the framework of neuroanatomic circuits hypothesized to participate in the pathophysiology of depressive disorders (3,23). More recently, Lauterbach et al (47) proposed an elaborated model to explain the contribution of posterior pallidal lesions in depressive pathophysiology.

Further evidence of an anatomic basis of poststroke depressive disorders stems from the analysis of the profile of neuropsychologic disorders. Apart from deficits that can be attributed to aphasic disorders (verbal fluency and verbal memory performance), the most prominent disorders were found in frontal lobe associated-functions (nonverbal working memory, fluency, reaction times, and error control in attentional performance tasks with higher cognitive load). Even subjects without frontal lobe involvement in lesion location exhibited medium severe to severe frontal lobe-associated deficits. These findings are consistent with a series of position emission tomography/magnetic resonance imaging studies which demonstrated (pre-) frontal lobe pathology (reduced blood flow/reduction in cortical volume) in depressive subjects without (54–56) and with stroke (18). Our data indicate that both depressive disorders and frontal lobe dysfunction might be associated with basal ganglia pathology. Due to the study design and the focus on a highly selected sample of depressive patients, the data give no indication of whether neuropsychologic disorders were related to brain infarction or to depressive alterations.

There is a wide consent in the literature that depressive disorders after stroke have a negative impact on the patients' potential of recovery. With regard to the etiopathogenesis of poststroke depressive disorders, however, there is still broad controversy on the biological basis of depressive disorders, and many studies fail to identify neuroanatomic correlates of depressive disorders. The major limitation in the interpretation of studies focussing on poststroke depression is posed by methodologic problems (4). A primary problem is the reliability and validity of the assessment of depression in patients who have had a stroke. Neurologic, neuropsychologic, and communication problems may mask or mimic depressive symptoms (16), and in many studies patients with aphasia were excluded from the data analysis. Our data, however, show that somatic or behavioral items of the DSM-III-R or depression rating scales do not necessarily reflect the neurologic or neuropsychologic condition of the patients. We found no significant correlation between depressive symptoms such as lack of energy/reactivity or concentration disorders and neuropsychologic measures of cognitive speed. Subjects with symptoms of disinhibition in tasks of attentional performance (response selection/inhibition, error control) showed no higher scores in the irritability items of depression scales. Furthermore, only five patients with major depressive disorders received antidepressive drug treatment that started within the same week of neuropsychologic investigations. Therefore, we assume that medication did not influence the neuropsychologic performance.

These findings support the hypothesis that depressive disorders after stroke represent distinguishable psychopathologic entities. The validity and reliability of the diagnosis of poststroke depression can be increased by the use of structured clinical interview, different self-rating and observer-rating scales (covering a range of different depressive symptoms) and the careful control of confounds or covariates (such as the neurologic or neuropsychologic condition or drug treatment). Our experience (23), as well as the experience of other groups (57), shows that even mild to moderate aphasia is not necessarily an exclusion criterion in studies of poststroke depression.

A second major obstacle to the interpretation of the association of lesion location and poststroke depression is posed by the method of lesion analysis. The analysis of lesions to the subcortical gray matter often depends on data reconstruction and planimetric measurements as well as on analysis of the vascular supply of areas involved in lesion topography. In most studies, however, the investigation of lesion anatomy is based on superficial judgments by evidence.

Taken together, the results of the present analysis of depressive disorders in the postacute stage of stroke, based on a carefully selected and controlled patient sample, show that:

1) major depressive disorders are predominantly found in patients with left hemisphere strokes and constitute a distinguishable psychopathological entity;

2) type and severity of depression is not associated with number or degree of neurologic symptoms or impairment in activities of daily living; and

3) lesions to frontostriatal circuits seem to play a crucial role in the pathogenesis of some poststroke depression.

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