Depression in acute and chronic aphasia: symptoms, pathoanatomical-clinical correlations and functional implications

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Abstract

Depressive alterations were investigated in 21 acute and 21 chronic aphasic patients with single left sided strokes. The assessment of depression was based on a psychometrically evaluated German version of the Cornell Scale for Depression (CDS) and the Research Diagnostic Criteria (RDC). No significant difference was found concerning depression sumscores between the two aphasic groups. The acute group, however, exhibited significantly higher ratings in items related to physical signs of depression and disturbances of cyclic functions. Patients corresponding to the RDC-syndrome of major depression were only found in the acute group. Neither age, sex nor degree of hemiparesis discriminated the patients on the severity of depressive symptoms. In the acute patient group, nonfluency of aphasia was the only parameter that could be identified which had an effect on the mood symptom scores. A CT scan analysis in the acute patient group showed an association between the severity of depression and anterior lesions. A significant correlation was found between CDS sum-scores and the proximity of the anterior border of the lesion to the frontal pole of the hemisphere whereas the volume of lesions seemed to have no effect on depressive alterations in acute aphasic patients. Superimposition of the lesions of the aphasic patients with major depressive disorders showed a common subcortical lesion area involving putaminal and external pallidal structures.

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In the past decade, depressive mood changes after stroke gained importance both for our understanding of the mechanisms underlying impairment and for rehabilitation. Despite intensive research concerning aetiology, pathogenesis and differential diagnosis of depressive disorders following brain insults, the results and conclusions of the various studies differ greatly. The extent of the variation in the data on the prevalence of post-stroke depression (PSD) indicates that heterogeneous and in some aspects incompatible research designs were applied. Lipsey *et al*[1] found "clinically significant depression" to occur in 30—60% of patients suffering from

the consequences of brain infarction, whereas House *et al*[2] reported a prevalence of "major depressive disorders" in only 11% one month and 5% one year post stroke. The reliability and comparability of various investigations are hampered by differences in study design two of which are briefly outlined:

1) Research strategies are based upon at least three different theories concerning aetiology and pathogenesis of depressive changes following stroke. Recent research focusing on PSD as a correlate of the neuropathological consequences of stroke describes depression as a mental disease in the terminology of psychiatric classification systems.[3] In contrast to this view, the concept of "grief response"[4] views the depressive reaction as a natural, non-pathological phase of the coping process whereas the concept of "(depressive-) catastrophic reaction"[5][6] describes an entirely different entity of emotional-affective reactions.

2) In a number of studies, depressive changes following stroke have been evaluated using standardised instruments taken from psychiatric research on depressive disorders. Furthermore, psychiatric classification systems were often used (for example, DSM-III-R[7]; or RDC).[8] Only exceptionally, validity and applicability have been investigated for stroke patient populations.

This aspect is of special importance for the assessment of depressive changes in aphasic patients. It seems highly doubtful that patients with relevant (written language) comprehension impairment can be reliably and validly evaluated by standard self rating scales or assessment procedures that rely on intensive verbal communication. Consequently, asphasic patients, although a quantitatively important sub-population of stroke patients, have frequently been excluded from studies concerned with PSD.

The present state of research on depression in stroke, and in aphasic patients in particular, is hall-marked by the contributions of Robinson and Starkstein, who claim that major depressive disorders are a frequent result of cerebrovascular insults that may already be present in the acute phase and usually last for one to two years.[9][11] Further results indicate that depressive changes are more frequent with left hemisphere lesions and that their degree correlates negatively with the distance between the frontal pole and the anterior border of the lesion, both with respect to its cortical and subcortical aspects.[12][13] However, House *et al*[2] and others[14][15] were unable to replicate the

significant correlation of degree of depression with the proximity of the lesion to the frontal pole.

This study compares depressive changes in acute and chronic aphasic patients. The study aimed: 1) at differences in degree and profile of depressive symptoms, and 2) at associations of depressive changes with type of aphasia, lesion localisation and volume.

Patients and methods

Patients

Twenty one patients with acute (less than 3 months post onset) and 21 with chronic (more than 6 months post onset) aphasia of vascular origin were included. Selection criteria were:

1) Aphasia diagnosed on the basis of the Aachen Aphasia-Test.[16]

2) Vascular aetiology (ischaemic or secondary haemorrhagic stroke).

3) Presence of a single demarcated lesion in the CT.

4) No history of alcohol or drug abuse or psychiatric disorder.

The groups were comparable for type and degree of language deficit, age, income and educational status. Table 1 gives details of the clinical and demographic data of both patient groups.

Methods

Psychiatric assessments

A psychometrically evaluated German adaptation of the Cornell Depression Scale (CDS),[17] was used. The CDS was originally constructed for the assessment of demented patients and has been evaluated for this population. The scale consists of 19 items that were selected to take into account the specific cognitive and somatic impairments of patients with brain disease. Five levels of observation are included: A) mood related signs; B) behavioural disturbances; C) physical signs; D) cyclic functions and E) ideational disturbances. The instrument focuses on observers' ratings but also includes information derived from a short interview and case history. The interrater-reliability was good for various

aphasic populations and rater groups (Spearman's Rho = 76-84 (p < 0·01); Kendall's W = 0·75–0·85 (p < 0·001)). Its internal consistency (Cronbach alpha = 0·80, KR-20 = 0·82) and congruent validity (compared with the Montgomery-Åsberg-Scale[18] (Spearman's Rho = 0·81 p < 0·01) reflect a high methodological quality of the instrument for the investigation of aphasic patients. In addition, the power to differentiate degrees of impairment (discriminant validity: Mann-Whitney U: p = 0·0002-0·0182) seemed satisfactory.

All patients were classified for depressive disorders on the basis of the RDC-classification[8] which was used to allow for a comparison of our data with the psychometric evaluation of Alexopoulos et al.[17]

Radiological assessments

Only CT scans of the acute aphasic patients are considered in our investigation. Considerable differences in slice thickness and angle precluded comparative analysis of the CT scans in the chronic group. The scans of the acute patients group were performed about 15 days post stroke in standardised slices without contrast enhancement. As described by Poeck et al,[19] site and extent of lesion was measured in the original CT photographs and then transposed into a set of 9 standardised grids based on the brain sections of Matsui and Hirano.[20] These grids were analysed by a computer program developed in our laboratory that computes lesion volumes and produces superimposition diagrams and analyses.

The average distance from the frontal pole in per cent of overall anterior-posterior distance was calculated and the lesions were classified as anterior or posterior based on the approach of Robinson et al.[12] For each case, these data were collected independently by two CT evaluators. The interrater-reliability was highly satisfactory both for evaluation of the original scans and the standard templates (Spearman's Rho = 0·96; p < 0·001).

Data analysis was conducted by non-parametric procedures (Mann-Whitney-U-Tests, rank correlations, values corrected for ties) with the SPSS-X statistical package.

Results

Psychiatric status

For the acute and the chronic group, the analysis of the depression-scores revealed skewed distributions (acute patients: CDS: Mdn = 6, Range = 0–21; chronic patients; CDS: Mdn = 5, Range = 0–13). Numerically higher scores were found with the acute patients, but statistical significance was not reached (Mann-Whitney U-test: CDS: U = 195, p = 0·5193). With the exception of a non-significant higher frequency with the item "sadness" in the acute group (66·6% acute vs 42·8% chronic patients), no differences were found for the CDS-level of observation "mood related signs". Symptoms of anxiety were noted in about half of the patients in both groups (42·8% acute vs

Table 1   Clinical data of the acute and chronic patient groups

	Acute patients	Chronic patients
Number of patients	21	21
Age (Median/Range [years])	62/26–81	62/27–79
Sex (Female/Male)	6/15	10/11
MPO (Median/Range [months])	1·0/0·5–2·5	35/7–132
Type of Pathology:		
Ischaemic	15	17
Secondary haemorrhage	6	4
Type of Aphasia[1]:		
Amnestic	2	2
Wernicke	5	5
Broca	7	8
Global	3	4
Non Classifiable	4	2
Hemiparesis	16	11
Apraxia	6	5

[1]according to Aachen Aphasia-Test criteria (AAT[16]).

47·6% chronic patients). Lack of reactivity in response to pleasant events was rarely observed. There was also no significant difference between the acute and chronic group for symptoms of "behavioural disturbances". Half of the chronic aphasics exhibited symptoms of agitation and unrest (47·6% chronic vs 28·6% acute patients; ns), whereas more than half of the acute patients showed psychomotor retardation (61·9% acute vs 52·4% chronic patients). The "physical signs" of loss of weight and appetite were significantly more frequently observed in patients with acute aphasia. The most prominent symptom of this group is "lack of energy", which was exhibited by a majority of patients from both groups, although more frequently by the acute aphasics (71·4% acute vs 52·4% chronic aphasics; ns). The statistically most marked differences between the two groups were found for "disturbances of cyclic functions". With each symptom 20–25% of the acute, but less than 5% of the chronic aphasics received positive ratings ("Diurnal variation of mood": 28·6% acute vs 4·8% chronic patients; p < 0·05; "Difficulty falling asleep": 23·8% acute vs 4·8% chronic patients; ns.; "Multiple awakenings": 28·6% acute vs 0% chronic patients; p < 0·01; "Early morning awakening": 28·6% acute vs 0% chronic patients; p < 0·01). No significant difference between groups occurred for the level of "ideational disturbances": Suicidal ideas, self depreciation and pessimism were more frequently noted with the chronic patients. Mood congruent delusions were exhibited by one acute and one chronic aphasic.

A comparison of the CDS profiles revealed that the patients with chronic aphasia received higher ratings with items that can be interpreted as symptoms of a depressive reaction to stroke-related impairment (physical complaints, suicidal ideas, poor self-esteem, pessimism). The higher scores of the acute group for physical signs of depression and cyclic dysfunctions cannot be interpreted unequivocally. They could represent endogenously induced symptoms of depression or reflect reactions to either acute severe disease or to the special inpatient conditions. However, the acute fluent patients with aphasia who were subject to the same inpatient conditions as the acute nonfluent patients exhibited significantly lower scores for "physical signs" and disturbances of "cyclic functions".

The relationship between speech pathology, neurological impairment and psychiatric status
An analysis of differences in the distribution of CDS sumscores for patient groups divided according to sex, age, and degree of hemiparesis revealed no significant effects. Type of aphasia (fluent (Wernicke and anomic) vs nonfluent (Broca and global)) was the only significant parameter which separated the aphasic patients with respect to the degree of depression. Patients with nonfluent aphasia exhibited significantly higher depression

scores (all patients: p = 0·0074; Mann-Whitney U-Test). Closer analysis revealed that this difference is only valid for the acute patients (p = 0·0014), but breaks down when only the chronic aphasic patients are considered (p = 0·9317).

All patients were then classified according to the RDC-criteria into the categories of "no depressive disorder", "minor depressive disorder", "probable major depressive disorder" and "definite major depressive disorder". This analysis supports the findings obtained with the CDS sumscores. In the acute group, 7 patients with nonfluent aphasia and one patient with non-classifiable speech pathology showed depressive disorders, 5 of which fulfilled the criteria for definite major depression. In the chronic group, no patient was rated as having probable or definite major depression. Minor depressive disorders were found in 3 nonfluent and 1 fluent chronic aphasic.
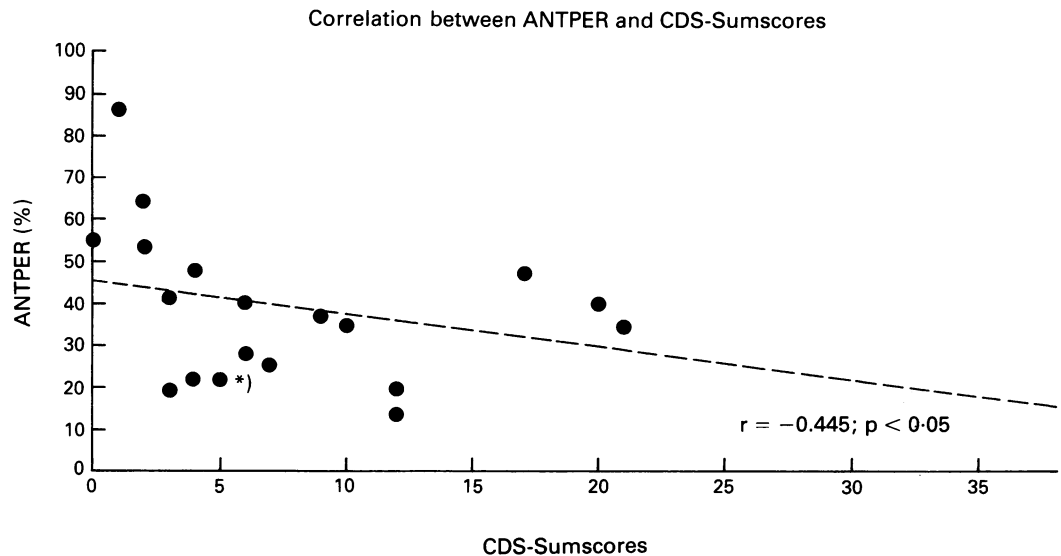
CT scan findings
The patients included in the acute group had been investigated by CT scan 9–43 days after stroke (MDN: 15 days). The presence of a well-defined lesion was required for inclusion. Three patients showed predominantly cortical lesions without involvement of the subcortical nuclei, in 7 the cortex was spared, and in 11 patients both cortical and subcortical structures were involved. A total of 15 patients had suffered from ischaemic infarction and 6 from secondary cerebral haemorrhage. (1 patient was excluded from further analysis because of marked midline shift and left sided ventricular enlargement). The median distance of the anterior lesion boundary from the frontal pole was calculated 36·1% (Range = 13·1%–86·2%) and the median lesion volume in per cent of forebrain volume was calculated 2·75% (Range = 0·8%–19·7%). Unsurprisingly, all patients with posterior and none with anterior lesions exhibited fluent aphasia. Three patients with anterior lesions were non-classifiable by the fluent/nonfluent division, and two nonfluent patients showed non-classifiable lesions.

Figure 1 shows a scattergram of the correlation between CDS sumscores and the proximity of the lesion to the frontal pole.

The correlation between the proximity of the lesion and the CDS sumscore was numerically low but significant (Rho = 0·445 (p < 0·05). Its value was considerably below correlations reported by the Baltimore group[10 12 21] and others), but higher than the correlation reported by House et al.[2] Our data are comparable to those calculated by Starkstein et al[13] in a combined analysis of cortical and subcortical lesions.

House et al[2] suggested that the proximity effect could represent an epiphenomenon of a lesion volume effect with larger lesions tending to coincide with more anterior boundaries. In our study, no interaction was found between lesion volume and proximity of the lesion (Spearman's Rho = 0·043; ns). There was also no correlation between lesion

Figure 1 Scatterplot of the correlation between proximity of the lesion and CDS-sumscores.

volume and degree of depressive changes (Rho = 0·152; ns). These results suggest that the presence of a depressive disorder rather reflects the effect of a specific lesion type or location than a volume effect.

In fig 2, the lesions of those 6 patients with acute aphasia that fulfilled the RDC-criteria for "probable or definite major Depression" (MD) were superimposed and compared with a superposition of 6 other acute patients without signs of a depressive disorder that had lesions of comparable size (NSD). This second group consisted of patients with a CDS sumscore of less than 5 (maximum = 38) who exhibited no symptoms of depressive mood (that is, no positive ratings in the items "sadness" and "loss of interest") and who did not comply with the RDC criteria of major or minor depression.

The anatomical lesions were analysed by comparison with the templates of Damasio and Damasio.[22] Figure 2 shows that the MD group consisted of patients with predominantly fronto-parietal lesions with a maximal overlap in paramedian subcortical structures. Conversely, the NSD patients showed a rather diffuse distribution of more posteriorly located lesions without clear overlap and the core lesion of the MD aphasics was hardly involved at all.

The anatomical analysis of the MD core lesion suggests that it includes basal aspects of the lentiform nucleus, the medial part of the posterior limb of the internal capsule and large parts of pallidum and putamen, corpus nuclei caudati and parietal periventricular white matter. The thalamus is probably spared, but due to the low resolution of the grid matrix, an involvement of the most lateral aspects of the ventrolateral nuclei cannot be ruled out. In summary, the superimposed lesions of patients with acute aphasia with major depression show an area of overlap in the region of the left lenticular nucleus. This overlap area is supplied by lateral and medial lenticular branches of the middle cerebral artery and the anterior choroideal artery (according to Damasio and Damasio[22] and Ghika et al[23]).

Discussion

We found no overall difference in degree of depressive changes between two groups of patients with acute and chronic aphasia that were comparable for the degree of language impairment. However, there were significant differences for the profile of depressive symptoms: those with acute aphasia received significantly higher scores on ratings of "physical signs" of depression and "disturbances of cyclic functions".

An obvious first approach at interpretation, especially for the acutely aphasic patients, would be to assign the depressive symptomatology to an acute depressive reaction towards acute severe illness/impairment or as an artefact of the inpatient condition. However, the symptom profile of the acute patients fulfilling the criteria of probable or definite major depression in our study is parallel to the patterns described by Lipsey et al,[24] for stroke patients with major depression. These authors were able to demonstrate that there were no significant differences between the profiles of depressive symptoms related to stroke and functional major depressive disorders. We assume that post stroke depression in *acute* patients cannot be interpreted on the basis of "increased emotionalism"[2] but is parallel to the psychiatric disorder of major depression.

Patients corresponding to the RDC criteria of major depression were exclusively found among the acute aphasic patients and major depressive disorders were significantly associated with nonfluency of aphasia. This finding supports similar results of previous studies.[5][25] However, Gainotti[5] and Robinson and Benson[25] interpreted their findings differently.

□ > 4 Patients

▓ > 3 Patients

▤ > 2 Patients

M D   **N S D**
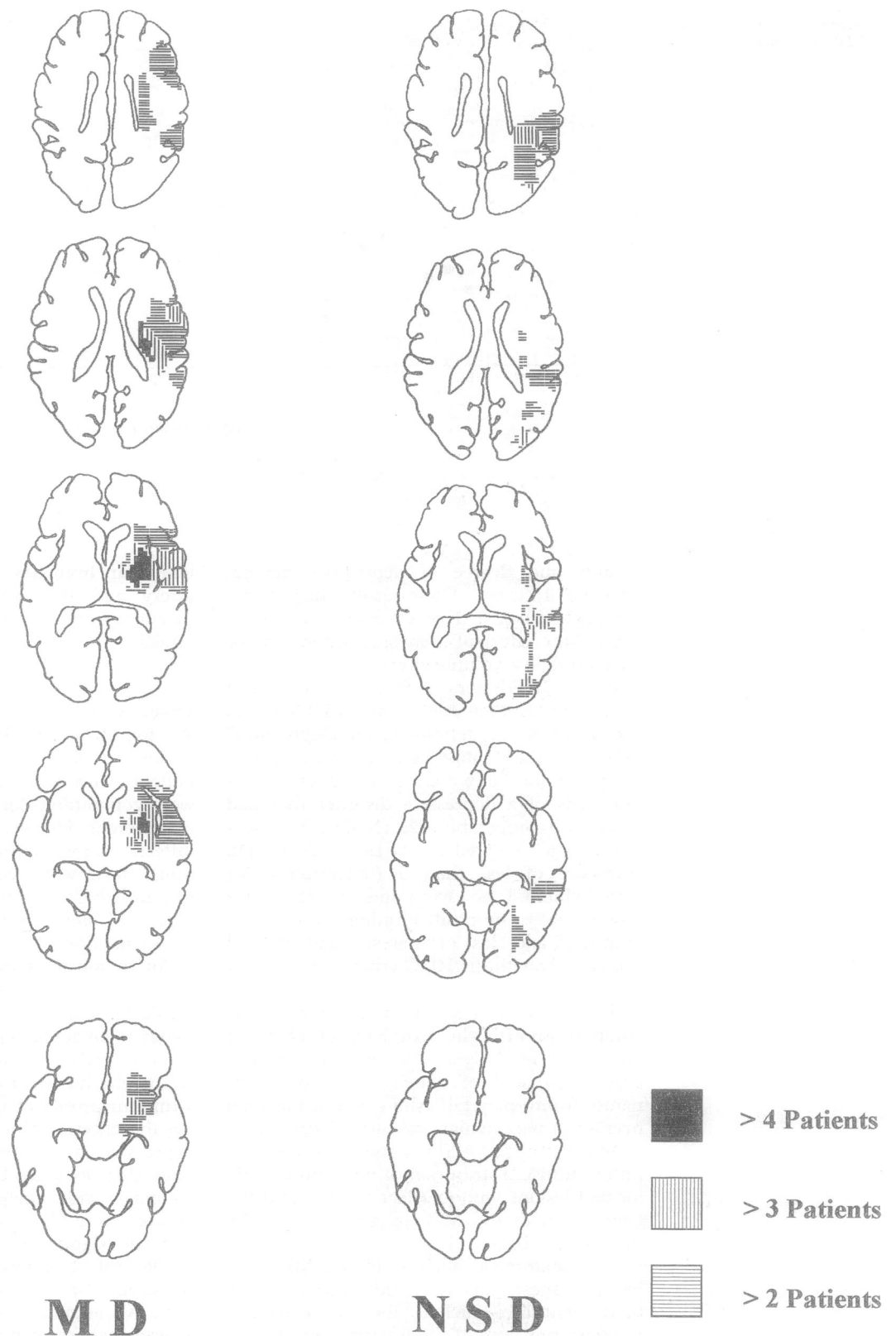
Gainotti's concept of "(depressive)-cata-strophic reactions" rather corresponds to the "increased emotionalism" of House et al.[2] With this line of interpretation the higher incidence and greater degree of depressive symptoms in patients with anterior lesions could be explained as psychoreactive to their more distressing nonfluent language disorders (compared with patients with posterior lesions and fluent language disorder) and hemiparesis. At least in the postacute and chronic stages of aphasia, psychosocial and coping factors are relevant for the development of reactive depression. We have discussed these interactions in a multitime and multifactor model of depression in aphasia elsewhere.[26]

Conversely, Robinson et al assume an anatomically based coincidence of depression and nonfluent aphasia. Our CT scan analysis

for the acute aphasic patients supports this second interpretation. We found a low but significant correlation between the anterior lesion boundary and the degree of depression in acute aphasia, but no interaction with lesion size.

The following pathogenetic considerations are based only on the results of our acute patients. The correlation between degree of depression and the proximity of the lesion as such gives only scanty evidence on the underlying anatomical or physiological basis of depressive disorders in aphasic stroke patients. Detailed analysis reveals that the correlation mainly stems from the cortical extent of lesions of patients suffering from infarctions including the anterior group of branches of the middle cerebral artery. With respect to the anatomical structures involved, all acute aphasic patients with "Major Depression" in our study had either entirely subcortical CT lesions (N = 3) or lesions involving both subcortical and cortical structures (N = 3). Superposition of the lesions of this patient group revealed a core lesion area in the region of the left basal ganglia. The low correlation between degree of depression and the proximity of the lesion may therefore merely reflect a secondary aspect of the pathology that caused a lesion in this core area but have no further explanatory value of its own on the pathogenesis of post-stroke depression. If depressive disorders in acute aphasic patients result from certain focal subcortical lesions, then the lesion volume cannot have much relevance in pathogenesis. In accordance with this assumption, no correlation was found between lesion size and degree of depression.

The view that post-stroke depression results from specific subcortical damage is collaterally supported by modern models of depression pathogenesis. Robinson *et al*[12 13 21] favour the monoamine deficit hypothesis as a pathophysiological explanation of post-stroke depression. They point out that more anteriorly located lesions affect noradrenergic and serotonergic projections ascending from the tegmentum pontis to the forebrain cortex more proximally and therefore to a greater extent than posterior lesions. This hypothesis is supported by studies on neurochemical changes of receptor sensitivity for biogenic amines after stroke.[27 28] These recent findings, however, contribute little to our understanding of the possible role of the subcortical nuclei in the pathogenesis of depression in left hemisphere stroke.

Another line of evidence indicates that lesions of subcortical structures could indeed be of crucial importance in the pathogenesis of post-stroke depression. In their study of subcortical aphasia, Alexander and Lo Verme[29] reported marked or severe depression in two of nine cases with thalamic lesions and in four of six patients with putaminal pathology. Starkstein *et al*[13] established an interaction between the anteriority of the lesion and the degree of depression also for patients with left hemisphere subcortical

lesions. A reanalysis of their data[3] revealed a significantly higher prevalence of major depressive disorders in patients with basal ganglia than with thalamic lesions. Furthermore, these authors were able to show that patients with left basal ganglia lesions exhibited more severe depressive changes than patients with right sided basal ganglia or thalamic lesions of either side.[30] Finally, Starkstein *et al*[31] reported that basal ganglia lesions occurred more frequently in patients with major depression than in a control group suffering from generalised anxiety disorders. The authors offer a number of explanatory models for these findings: a) subcortical lesions could cause prefrontal hypometabolism as a remote effect; b) ascending monoaminergic pathways could be affected; c) the basal ganglia lesion itself could be related to depression genesis.

The latter hypothesis is supported by theories concerning the role of the ventral striatum as a central component of a cortico-striato-pallido-thalamo-cortical loop in the regulation of emotional processes. The structure of the "anterior cingulate loop" of Alexander *et al*[32] predicts that the interruption of the striato-pallidal pathway would lead to dysregulations of emotional functions. The more elaborated model of Swerdlow and Koob[33] contains three functionally independent loop systems between limbic cortex, basal ganglia, the dorsomedial nucleus of the thalamus and brainstem structures. The core lesion of patients with major depression described in this study interrupts both ascending dopaminergic pathways from the ventral tegmentum and striato-pallidal projections. In the Swerdlow and Koob model, it would lead to a tonic disinhibition of the cortico-thalamo-cortical reverberation loop and, as the behavioural correlate of the neurochemical dysregulation, to "psychomotor retardation, paucity of affect, cognitive perseveration, and anhedonia in depression" (Swerdlow and Koob[33]).

Swerdlow and Koob's model is also consistent with numerous reports that isolated thalamic lesions may result in multiple neuropsychological dysfunctions but only rarely in depressive changes (for example,[34]) and the improvement of depression following dorsomedial thalamotomy.[35]

Although the results of our study are hampered by a number of reservations, especially small sample size, a number of conclusions can be drawn: 1) differences in the depressive symptom profile between acute and chronic aphasics and the presence of a specific core lesion with *acute* aphasic patients with major depressive disorder indicate an endogenous genesis of depression in acutely aphasic stroke patients. Aphasia and depression can be viewed as coincident consequences resulting from a common type of underlying vascular pathology; 2) the analysis of the common lesion found in acute aphasic patients with major depression indicates a special role of the basal ganglia and their surrounding white matter in the pathogenesis of poststroke left

hemisphere depression; 3) moderately and severely aphasic patients are an important subpopulation in investigations of poststroke depression that must not be disregarded by exclusion for methodological reasons.

1 Lipsey JR, Robinson RG, Pearlson GD, Rao K, Price TR. The dexamethasone suppression test and mood following stroke. *Am J Psychiatry* 1985;142:318–23.

2 House A, Dennis M, Warlow C, Hawton K, Molyneux A. Mood disorders after stroke and their relation to lesion location—A CT scan study. *Brain* 1990;113:1113–29.

3 Starkstein SE, Robinson RG. Aphasia and depression. *Aphasiology* 1988;2:1–20.

4 Tanner DC, Gerstenberger DL. The grief response in neuropathologies of speech and language. *Aphasiology* 1988;2:79–84.

5 Gainotti G. Emotional behavior and hemispheric side of the lesion. *Cortex* 1972;8:41–55.

6 Benson DF. *Aphasia, alexia, and agraphia.* New York: Churchill Livingstone 1979: 174–80.

7 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders,* 3rd ed. Washington, DC: American Psychiatric Association, 1987.

8 Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: Rationale and reliability. *Archives of General Psychiatry* 1978;35:773–82.

9 Robinson RG, Starr LB, Kubos KL, Price TR. A two-year longitudinal study of post-stroke mood disorders: findings during the initial evaluation. *Stroke* 1983;14:736–41.

10 Robinson RG, Starr LB, Lipsey JR, Rao K, Price TR. A two-year longitudinal study of poststroke mood disorders: dynamic changes in associated variables over the first six months of follow-up. *Stroke* 1984;15:510–17.

11 Robinson RG, Bolduc PL, Price TR. Two year longitudinal study of poststroke mood disorders: Diagnosis and outcome at one and two years. *Stroke* 1987;18:837–43.

12 Robinson RG, Kubos KL, Starr LB, Rao K, Price TR. Mood disorders in stroke patients—importance of location of lesion. *Brain* 1984;107:81–93.

13 Starkstein SE, Robinson RG, Price TR. Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. *Brain* 1987;110:1045–59.

14 Sharpe M, Hawton K, House A, *et al.* Mood disorders in long-term survivors of stroke: Associations with brain lesion location and volume. *Psychological Medicine* 1990;20:815–28.

15 Wade DT, Legh-Smith JE, Hewer RA. Depressed mood after stroke: A community study of its frequency *Br J Psychiatry* 1987;151:200–5.

16 Huber W, Poeck K, Weniger D, Willmes K. *Aachener Aphasie Test.* Göttingen: Hogrefe, 1983.

17 Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Use of the Cornell Scale in nondemented patients. *J Am Geriatric Soc* 1988;36:230–6.

18 Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9.

19 Poeck K, De Bleser R, von Keyserlingk D. Computed tomography localization of standard aphasic syndromes. In: Rose FC, ed. *Progress in aphasiology.* New York: Raven, 1984:71–90.

20 Matsui T, Hirano A. *An atlas of the human brain for computerized tomography.* New York: Igaku-Shoin, 1978.

21 Robinson RG, Szetela B. Mood change following left hemispheric brain injury. *Ann Neurol* 1981;9:447–53.

22 Damasio H, Damasio AR. *Lesion analysis in neuropsychology.* New York: Oxford University Press, 1989.

23 Ghika JA, Bogousslavsky J, Regli F. Deep perforators from the carotid system—Template of the vascular territories. *Arch Neurol* 1990;47:1097–100.

24 Lipsey JR, Spencer WC, Rabins PV, Robinson RG. Phenomenological comparison of poststroke depression and functional depression. *Am J Psychiatry* 1986;143: 527–9.

25 Robinson RG, Benson DF. Depression in aphasic patients: frequency, severity, and clinical-pathological correlations. *Brain and Language* 1981;14:282–91.

26 Herrmann M, Wallesch CW. Depressive changes in stroke patients. *Disability and Rehabilitation* (in press)

27 Mayberg HS, Robinson RG, Wong DF, *et al.* PET imaging of cortical S2-serotonin receptors after stroke—lateralized changes and relationship to depression. *Am J Psychiatry* 1988;145:937–43.

28 Barry S, Dinan TG. Alpha-2 adrenergic receptor function in post-stroke depression. *Psychological Medicine* 1990; 20:305–9.

29 Alexander MP, Lo Verme SR. Aphasia after left hemispheric intracerebral hemorrhage. *Neurology* 1980;30: 1193–202.

30 Starkstein SE, Robinson RG, Berthier ML, Parikh RM, Price TR. Differential mood changes following basal ganglia vs. thalamic lesions. *Arch Neurol* 1988;45: 725–30.

31 Starkstein SE, Cohen BS, Fedoroff P, Parikh RM, Price TR, Robinson RG. Relationship between anxiety disorders and depressive disorders in patients with cerebrovascular injury. *Arch Gen Psychiatry* 1990;47:246–51.

32 Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Ann Rev Neurosci* 1986;9:357–81.

33 Swerdlow NR, Koob GF. Dopamine, schizophrenia, mania, and depression: Toward a unified hypothesis in cortico-striato-pallido-thalamic function. *Behavioral and Brain Sciences* 1987;10:197–245.

34 Graff-Radford NR, Eslinger PJ, Damasio AR, Yamada T. Nonhemorrhagic infarction of the thalamus: Behavioral, anatomic, and physiologic correlates. *Neurology* 1984; 34:14–23.

35 Spiegel EA, Wycis HT, Freed H, Orchinik C. The central mechanism of the emotions (Experiences with circumscribed thalamic lesions). *Am J Psychiatry* 1951;108: 426–32.