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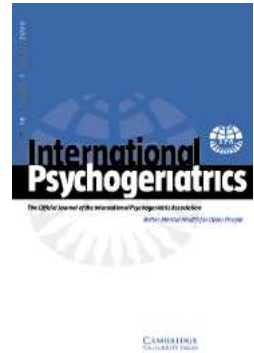
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Focal or generalized vascular brain damage and vulnerability to depression after stroke: a 1-year prospective follow-up study

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ABSTRACT

Background: Both the lesion location hypothesis and the vascular depression hypothesis have been proposed to explain the high incidence of depression in stroke patients. However, research studying both hypotheses in a single cohort is, at present, scarce.

Objective: To test the independent effects of lesion location (left hemisphere, anterior region) and of co-occurring generalized vascular damage on the development of depression in the first year after ischemic stroke, while other risk factors for depression are controlled for.

Methods: One hundred and ninety consecutive patients with a first-ever, supratentorial infarct were followed up for one year. CT was performed in the acute phase of stroke, while in 75 patients an additional MRI scan was also available. Depression was assessed at 1, 3, 6, 9, and 12 months after stroke using self-rating scales as screening tools and the SCID-I to diagnose depression according to DSM-IV criteria.

Results: Separate analyses of the lesion location hypothesis and the vascular depression hypothesis failed to reveal significant support for either of these biological models of post-stroke depression. Similar negative results appeared from one overall, multivariate analysis including variables of both focal and generalized vascular brain damage, as well as other non-cerebral risk factors. In addition, level of handicap and neuroticism were independent predictors of depression in this cohort, as has been reported previously.

Conclusion: This study supports neither the lesion location nor the vascular depression hypothesis of post-stroke depression. A biopsychosocial model including both premorbid (prior to stroke) vulnerability factors, such as neuroticism and (family) history of depression, as well as post-stroke stressors, such as level of handicap, may be more appropriate and deserves further study.

Key words: mood, affective, poststroke, cerebrovascular, risk, longitudinal, epidemiology, biopsychosocial

Introduction

During the last two decades extensive research has tried to identify the etiological role of cerebral damage in the development of depression in stroke patients (Aben *et al.*, 2001). Most attention has been paid to the “lesion location hypothesis”, which suggests that post-stroke depression (PSD) is directly caused by focal damage to brain regions involved in the mood regulatory system. As an alternative, the so-called “vascular depression hypothesis” emphasizes the role of generalized vascular brain damage in the development of depression in elderly patients.

Robinson was the first to report that left-hemisphere lesions and lesions located to the vicinity of the frontal pole were more frequently associated with PSD than lesions elsewhere in the brain (Robinson, 1998). Lateralized differentiation of the organization of emotions, the importance of frontal structures in the regulation of emotional behavior, and the characteristic distribution of noradrenergic axons via the white matter of the frontal lobes were proposed to underlie these preferential lesion locations in PSD. However, two recent systematic reviews on the relationship between the side of stroke and depression failed to confirm the association between left-sided strokes and depression (Carson *et al.*, 2000; Singh *et al.*, 1998). In a reaction to these publications, a meta-analysis was carried out, which suggested that in left-hemisphere stroke, PSD is related to the vicinity of the stroke lesion towards the frontal pole, whereas in right-hemisphere stroke this is not the case (Narushima *et al.*, 2003).

The vascular depression hypothesis has been postulated since different vascular diseases (stroke, coronary artery disease, myocardial infarction, diabetes, etc.), as well as vascular risk factors are associated with depression (Alexopoulos *et al.*, 1997). Krishnan was the first to present evidence that depression in patients with white matter lesions on MRI is characterized by older age, later age at onset of depressive disorder, and a different symptom profile (fewer feelings of guilt, more anhedonia and motor retardation) (Krishnan *et al.*, 1997). It may be considered an extension of the lesion-location hypothesis,

emphasizing that not only single lesions but also an accumulation of (smaller) lesions may induce depression. However, in their cohort of 275 stroke patients, Vataja *et al.* did not find a risk increasing effect of white matter lesions on the incidence of PSD (Vataja *et al.*, 2001).

While the evidence for specific biological models for PSD is still conflicting, other factors that need not specifically be stroke-related should be taken into account. This is in line with the observation that the incidence of depression in the course of other non-cerebral diseases is also increased (MI, rheumatoid arthritis, cancer) (Honig and Van Praag, 1997; Robertson and Katona, 1997). In all these conditions, pre-morbid vulnerability to depression, dysfunctional coping skills and personality traits, reduced quality of life with disabilities and handicaps, and lack of social support may all contribute to the development of depression. Consistent with such a biopsychosocial model of depression, we have recently shown that the personality trait of neuroticism and the extent to which stroke patients become handicapped are independent risk factors for depression after stroke (Aben *et al.*, 2002a).

In this study, we studied the cumulative one-year incidence of PSD in 190 consecutive patients with a first-ever supratentorial infarct. Available CT or MR scans were used to evaluate focal lesion characteristics as well as the occurrence of generalized vascular damage. First, we tried to replicate the finding that left-frontal strokes increase the risk for PSD. Secondly, we studied the occurrence of generalized vascular damage as a risk factor for PSD. Subsequently, using the same cohort, these two factors were combined into one multivariate analysis including other well-established risk factors of depression, such as female sex, history of depression, neuroticism and level of handicap.

Methods

Patients

Between September 1, 1997 and September 1, 1999, 444 consecutive patients were diagnosed with a first-ever supratentorial brain infarct at the Emergency Department and the Outpatients Clinic of the University Hospital of Maastricht, the Netherlands. This University Hospital serves approximately 200,000 inhabitants and is the only hospital in the region.

Stroke was diagnosed by a neurologist according to the WHO criteria. (National Institute of Neurological Disorders and Stroke, 1990) Patients' data were entered into a prospective stroke registry (Maastricht Stroke Registry-MSR), which has been described in detail elsewhere (Boon *et al.*, 1994). The ischemic nature of stroke was verified by CT. Patients with other types of stroke (e.g. recurrent stroke, hemorrhage, or brainstem infarct) were not included in order to increase the homogeneity of the study groups.

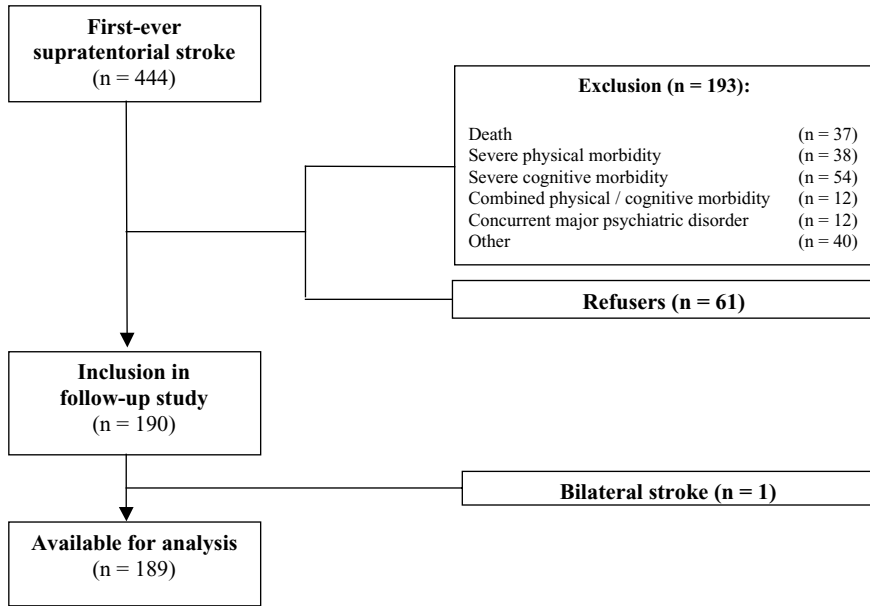


Figure 1. Patient selection and recruitment.

One hundred and ninety three (43.5%) patients were excluded. Exclusion of patients who were unable to communicate reliably (e.g., because of severe aphasia or cognitive dysfunction) was based on combined clinical judgment and Mini-mental State Examination (MMSE) and Frenchay Aphasia Screening Test (FAST) results (see below). Reasons for exclusion are shown in Figure 1.

Sixty-one of the remaining 251 eligible stroke patients refused participation (24.3%). Refusers were somewhat older than participants (72.4 ± 9.7 vs. 68.6 ± 11.7 years; $t(2) = 2.6$, $p = 0.01$). No sex difference was found between these two groups. Moreover, 35 refusers (57.4%) who were willing to fill out two psychiatric self-rating scales (SCL-90 and HADS, see below), did not report significantly more depressive symptoms than participants.

Thus, 190 stroke patients participated in the study. Major characteristics of this cohort are summarized in Table 1. All participants gave written informed consent. The study was approved by the Medical Ethics Committee of the University Hospital Maastricht.

CT and MRI scans

All patients had CT in the acute phase of stroke. Of a subgroup of 75 patients, an additional MRI scan was made as part of a research project on stroke and reactive hypertension (Boreas *et al.*, 2002). All scans were assessed by a neurologist (JL) who was blind to the clinical details of the stroke. Subsequently, discrepancies

Table 1. Demographic and outcome-related characteristics of stroke patients included in the analysis (n = 189)

	N = 189
Sex (female)	47.1%
Age, yrs (mean, sd; range)	68.5 (11.6; 36–89)
Level of education	
primary school	42.5%
junior secondary vocational education	25.5%
senior secondary vocational education	19.0%
(pre-)university education	13.0%
Living alone	35.9%
MMSE (median, min-max; % ≤ 23)	26 (16–30; 21.5%)
FAST (median, min-max)	27 (9–30)
Barthel (mean, s.d.; median)	17.5 (4.6; 20)
Rankin (mean, s.d.; median)	2.4 (1.2; 2)
Level of neuroticism (mean, s.d.)	30.1 (7.3)
Personal history of depression	21.8%
Family history of psychiatric disorders	36.0%

MMSE = Mini-mental State Examination (minimum score: 0, maximum score: 30); FAST = Frenchay Aphasia Screening Test (minimum score: 0, maximum score: 30); Barthel Index (completely dependent in Activities of Daily Living: 0, no disabilities: 10); Rankin (no handicaps: 0, bedridden: 5).

between CT or MR scorings and the clinical presentation of the stroke were detected and reconsidered.

Data were collected on lesion characteristics and (pre-existing) vascular brain damage (see below) using all available data from the MSR, CT and MR scans. If available, MR data had priority over CT data. If no “fresh” symptomatic infarct could be detected on any of the images, clinical data were used to determine type and side of the stroke lesion (de Jong *et al.*, 2003). This was the case in 51 of 113 patients who only had CT scans (45.1%) compared to only 4 patients with an MR scan (5.3%). The relatively high proportion of negative scans in patients with recent stroke is in line with other studies (Wardlaw *et al.*, 2003). In addition, the inter-rater agreement on the vascular imaging characteristics has been examined earlier by our group and was found to be excellent (κ -scores ≥ 0.79) (Rasquin *et al.*, 2004).

Lesion characteristics

Stroke type, lesion location, and lesion size were determined. Initially, stroke types were divided into cortical, subcortical, lacunar, centrum semi-oval or striatocapsular type. Because some of these types did not occur often, broad categories of territorial versus lacunar infarcts were made. Sub cortical and centrum semi-oval infarcts were considered territorial if their largest diameter

exceeded 15 mm. Infarcts including the cortex and striatocapsular infarcts were considered as territorial infarcts.

Lesion location was both expressed in terms of hemisphere involvement (left vs. right) and of involvement of the frontal region (further referred to as ‘anterior’ vs. ‘posterior’). In the case of territorial infarcts with a positive scan, the central sulcus was taken as the divider between the anterior and the remaining part of the brain. Striatocapsular infarcts were considered to involve the frontal circuitry. In case of a negative scan, clinical stroke symptoms were used to decide about frontal involvement. Stroke syndromes restricted to visual field deficits, visuo-spatial deficits, agnosia, apraxia, or other type of “higher cortical dysfunction” were listed in the “posterior” category, whereas those with frontal symptoms, such as Broca’s or mixed aphasia were considered as “anterior”. In the case of lacunar infarcts, involvement of the frontal region was considered to be represented by damage to the head of the caudate nucleus, striate nucleus, and anterior leg of the internal capsule. If no infarct could be detected on CT or MRI scan, all regular lacunar syndromes were considered to have a posterior localization because symptomatic lacunar infarcts are known to be mostly located in this region (Hupperts *et al.*, 1994) and it prevented us from falsely allocating infarcts without frontal involvement to the hypothesized high-risk group.

In the case of a territorial infarct, size was rated on a semi-quantitative basis as small, medium or large. For reasons of statistical power, data were subsequently dichotomized into small vs. medium/large.

Generalized vascular brain damage

Leukoaraiosis can be defined as an abnormal appearance of the subcortical white matter of the brain on neuroimaging. On CT, it is characterized by bilateral patchy or diffuse areas of low attenuation, while on T2 MR it presents as hyperintense areas in the white matter (Inzitari, 2003). On MR scans, such vascular white matter lesions were scored using the Fazekas scale. This scale separately rates the different types of hyper intense signal abnormalities surrounding the ventricles and in deep white matter. Periventricular hyper intensity (PVH) is graded as 0 = absence, 1 = ‘caps’ or pencil-thin lining, 2 = smooth ‘halo’, 3 = irregular PVH extending into the deep white matter. Deep white matter hyper-intensive signals (DWMH) are rated as 0 = absence, 1 = punctuate foci, 2 = beginning confluence of foci, 3 = large confluent areas (Fazekas *et al.*, 1987).

In case of CT data, leukoaraiosis was considered to be present if at least at one of both sides (periventricular or in deep white matter) patchy or diffuse areas of low attenuation were detected. Since CT scans are less sensitive to the detection of vascular white matter lesions, and in order to enable pooling of CT and MR data, we recoded the Fazekas ratings into one overall dichotomous measure of

leukoaraiosis (present vs. absent). Only in the case of confluent lesions, was leukoaraiosis rated as “present”.

Furthermore, asymptomatic (silent) infarcts were scored according to procedures described in more detail elsewhere (Rasquin *et al.*, 2004). On MRI and CT, these are characterized by circumscriptive low-density areas (hyperdense in T2 MRI), compatible with infarction, but without a history of any clinical signs or symptoms of stroke other than at study entry.

Initial assessment of depression

All patients were followed up during the first year after stroke. PSD was defined as an episode of major or minor depression according to DSM-IV criteria (American Psychiatric Association, 1994) on at least one assessment during the 1-year follow-up period. After one month, all patients were interviewed using both the depression section of the Structured Clinical Interview for DSM-IV (SCID-I-R) (First *et al.*, 1996) and the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). The SCID is a structured psychiatric diagnostic interview allowing for a DSM-IV diagnosis of major or minor depression. The HAM-D is a clinical rating scale that measures the severity of depressive symptoms. All interviews were administered by the same clinician (IA), who was trained to use these instruments. No formal test of inter-rater reliability was performed.

Follow-up assessment of depression

At 3, 6, 9, and 12 months after stroke, patients were asked to complete three psychiatric self-rating scales to screen for depression. These were the Beck Depression Inventory (BDI) (Beck *et al.*, 1961), the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), and the 90-item Symptom Check List (SCL-90) (Arrindell and Ettema, 1981). Cut-off levels were 9/10 for the BDI and 7/8 for both the depression and the anxiety subscale of the HADS. In the case of the depression subscale of the SCL-90, the threshold was 22/23 for men and 27/28 for women. The predictive validity of these instruments in this cohort was previously analyzed (Aben *et al.*, 2002b). The sensitivity of this screening procedure was shown to be 93.8% at the one-month assessment.

Patients whose scores exceeded the cut-off value for at least one of the self-rating scales were reinterviewed using the SCID and HAM-D in order to diagnose major or minor depression. In 50% of these cases, the interview was within two weeks; in 75% within 3–3.5 weeks.

In 33 patients the follow-up assessment of depression was incomplete, while the event of interest (depression) had not yet occurred. Of these, 16 withdrew their consent, 5 died, 8 had too severe co-morbidity, 1 was lost to follow-up, and 3 did not respond at the final assessment (12 months).

Potential confounders

Sex, age, personal history of depression, family history of psychiatric disorders, level of handicap, and neuroticism were predefined as potential confounders or effect modifications in the hypothesized relation between focal or generalized vascular brain damage and PSD.

Data concerning demographics, level of education, living situation, and family history of psychiatric disorders were collected on inquiry 1 month after stroke. Level of disability and handicap were rated at the same time using the Barthel Index (Mahoney and Barthel, 1965) and Rankin score (Rankin, 1957), respectively. Furthermore, personal history of depression was measured using the SCID-I-R, while the MMSE (Folstein *et al.*, 1975) and FAST (Enderby *et al.*, 1987) were administered to measure global cognitive functioning. Data on personal history of depression was missing in 4 cases, on family history of depression in 11 cases, and on Rankin score in 1 case.

Neuroticism was assessed one month after stroke, using the NEO Five Factor Inventory (NEO-FFI), (Costa and McCrae, 1985) which has been translated into Dutch (Hoekstra *et al.*, 1996). This self-report questionnaire consists of 60 statements covering the five main dimensions of personality: neuroticism, extraversion, openness to new experiences, agreeableness, and conscientiousness. Neuroticism has been related to depression most frequently (Enns and Cox, 1997) and is defined as a stable disposition to experience psychological distress across time and situations consisting of negative emotions such as fear, anger, and frustration (Costa and McCrae, 1985). Each statement is rated on a 5-point scale ranging from “strongly disagree” to “strongly agree”, resulting in total dimension scores between 12 and 60.

Non-response concerning the assessment of personality occurred in 36 patients (18.9%), either because of study withdrawal or difficulty completing the NEO-FFI.

Analysis

Since depressive outcome was measured prospectively on 5 different time-points during the 1-year follow-up, a survival analysis technique was applied by means of Cox regression. If data on depressive status on one assessment was missing, the patient was considered “not depressed” if the patient was not depressed at the former assessment and if the depressive status at the next assessment was validly measured. In all other situations, the case was excluded from further analysis from the time point of the next assessment onward.

Cox regression was used to analyze the relative hazard (HR) of the different measures of both focal and generalized vascular damage on the incidence of PSD (major and minor depression combined). First, hemisphere involvement

(left vs. right) and orientation towards the frontal pole (frontal region included vs. frontal region not included) were analyzed in an interaction model. Analogous, both measures of generalized vascular damage (leukoaraiosis and asymptomatic infarcts) were analyzed in an interaction model.

Secondly, a multivariate model was tested including measures on both lesion location and generalized vascular damage, as well as potential confounders (sex, age, personal history of depression, family history of psychiatric disorders, level of neuroticism, and level of handicap –i.e. Rankin score).

One case had bilateral stroke and was excluded from further analysis. In order to optimize the statistical power, missing data on dichotomous variables were imputed with value 0 (= absent), while missing data on continuous variables were imputed with the mean value of that variable. *Post-hoc* analyses were carried out to explore the consequences of this technique on the results by using list-wise deletion of cases with missing data on any of the variables in the equation. No interaction effects were hypothesized on an ‘*a priori*’ basis.

The output of the Cox analyses was checked for instability by influential cases and for violation of both the proportional hazards assumption and the assumption of linearity of effects. Where appropriate, Hazard ratios are given with their 95%-confidence intervals and 2-tailed *p*-values as: HR (95%-CI), *p*.

For group comparisons of descriptive sample characteristics, Student’s *t*-test was used in the case of continuous normally distributed variables. The χ^2 test was used for all dichotomous variables. Finally, one-way ANOVA was used to compare differences in HAMD scores between major depressed, minor depressed, and non-depressed patients. The level of significance was set at $p < 0.05$ (2-tailed) for all analyses. Where appropriate, results are given as means \pm SD.

Results

One-year cumulative incidence of depression

The 1-year cumulative incidence of depression was 38.7% (adjusted for cases with incomplete follow-up). Cross-sectionally, the incidence rates were 21.6% (41/190) at 1 month, 5.1% (7/137.5) at 3 months, 6.0% (7/117) at 6 months, 5.6% (6/107) at 9 months, and 7.1% (7/98) at 12 months. Of these, 41 patients (23.3%) met DSM-IV criteria for major depressive disorder and 27 (15.4%) met criteria for minor depressive disorder. The mean HAMD score was 19.2 ± 4.1 for the patients with major depression, 13.2 ± 4.3 for the patients with minor depression, and 7.3 ± 4.1 for the non-depressed patients. These differences were statistically significant ($F(2) = 198.2$; $p < 0.001$).

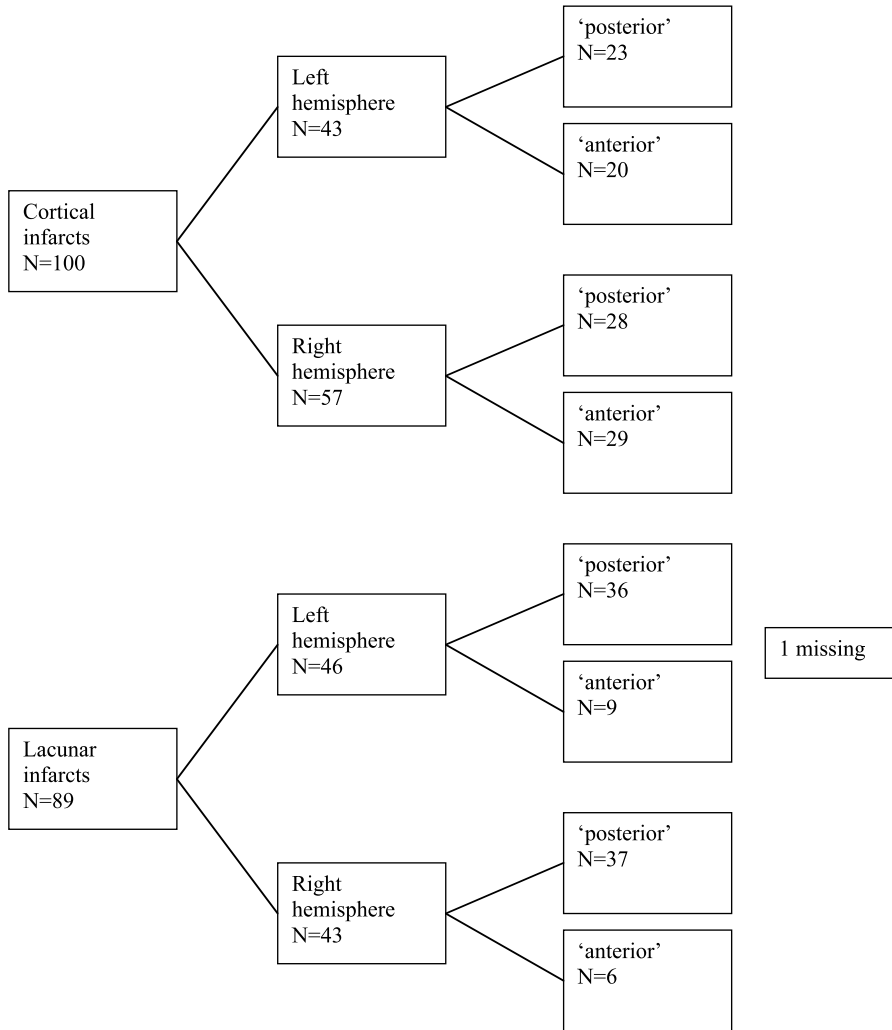


Figure 2. Distribution of lesion characteristics (hemisphere and frontal region involvement).

Distribution of measures of focal and generalized vascular damage

Of the 189 cases that were available for subsequent analysis on CT/MRI findings, 89 (47.1%) had left-sided strokes and in 100 patients (52.9%) the stroke was due to a territorial infarct. In 64 strokes (33.9%) the frontal region was involved. Figure 2 shows how these lesion characteristics were combined. Note the relatively low “anterior” to “posterior” ratio (15/73) in lacunar infarcts as compared to territorial infarcts (49/51). Size of infarct could only be rated in 75 of 100 cortical infarcts (25 were not visible on scan). Seventeen of these were rated as small, 47 as moderate and 11 as large.

Eighty-six patients (45.5%) showed one or more silent infarcts (i.e. not relating to clinical symptoms), while 59 patients had leukoaraiosis (31.2%). Of these patients, 48 had a positive score on both of these measures of generalized vascular damage, 11 only had leukoaraiosis, and 38 only had one or more silent infarcts. Signs of generalized vascular damage occurred with equal frequency between territorial and lacunar infarcts: 49/100 patients with a territorial infarct (49.0%) showed any sign of generalized vascular damage compared to 48/89 patients with a lacunar infarct (53.9%).

Lesion characteristics and generalized vascular damage: relation to depression

In an attempt to replicate the finding that left-sided strokes and/or strokes that involve the frontal region of the brain increase the risk of PSD, Cox regression was performed with side of lesion (left vs. right) and frontal-region involvement (“anterior” vs. “posterior”) as independent variables. No significant interaction effect of these lesion characteristics was found (left*anterior: HR 0.60 (0.20–1.79), $p=0.36$). Nor was there evidence of a risk increasing effect of one of the separate variables in a subsequent confounding model (left: HR 0.92 (0.57–1.49), $p=0.73$; anterior: HR 0.74 (0.43–1.25), $p=0.26$). In addition, the effect of infarct size could only be tested in 75 patients with a territorial infarct. Bivariate Cox regression analysis revealed no such effect (HR 0.73 (0.30–1.74), $p=0.47$).

Similarly, the attempt to replicate the finding that generalized vascular damage increases the risk of depression, failed to reveal an interaction effect for leukoaraiosis*asymptomatic infarcts: HR 1.93 (0.40–9.38), $p=0.42$. A subsequent confounding model also failed to reveal independent effects of leukoaraiosis (HR 0.91 (0.51–1.63), $p=0.75$) or asymptomatic infarcts (HR 1.30 (0.76–2.23), $p=0.34$) alone. Re-analysis of this model with one overall variable for generalized vascular damage confirmed the absence of a relationship with PSD.

In accordance with our suggestion that PSD should be considered as having a multifactorial path physiology, we subsequently tested one overall model including both the variables of focal and generalized vascular damage as well as non stroke-specific risk factors—sex, age, personal or family history of depression, neuroticism, and level of handicap.

Unexpectedly, in this multivariate model patients with “posterior” infarcts had a significant higher risk of depression than patients with strokes that involved the frontal region (see table 2). As expected from earlier analysis (Aben *et al.*, 2002a), from the variables that are not specifically stroke-related, neuroticism and level of handicap showed to be independent risk factors for PSD. In addition, a trend was shown for a positive family history of psychiatric disorders.

Table 2. Multivariate Cox regression models for factors of both focal and generalized vascular damage as risk factors for PSD after adjustment for potential other risk factors: all factors entered and forward stepwise procedure (n = 189)

W H O L E M O D E L	H R	9 5 % - C I	P
Territorial infarct (vs. lacunar)	1.09	0.63–1.88	0.77
Left hemisphere	1.11	0.66–1.86	0.70
Frontal region involved	0.52	0.28–0.98	0.04
Leukoaraiosis	0.79	0.42–1.51	0.48
Asymptomatic infarct(s)	1.28	0.73–2.24	0.39
Neuroticism (continuous scale)	1.07	1.02–1.11	0.003
Handicap (ordinal scale)	1.47	1.13–1.91	0.004
Family history of psychiatric disorder	1.53	0.92–2.53	0.10
Personal history of depression	1.30	0.71–2.35	0.40
Female sex	1.28	0.75–2.18	0.36
Age	0.99	0.97–1.02	0.63
S T E P W I S E M O D E L	H R	9 5 % - C I	P
Frontal region involved	0.56	0.32–0.98	0.04
Neuroticism (continuous scale)	1.08	1.04–1.12	<0.001
Handicap (ordinal scale)	1.43	1.14–1.79	0.002
Family history of psychiatric disorders	1.70	1.05–2.76	0.03

HR: Hazard Ratio.

Post-hoc, forward stepwise regression analysis was performed to optimize the model resulting in a four-factor model including “posterior” stroke, neuroticism, handicap, and family history of psychiatric disorders (table 2).

Further *post-hoc* analyses were performed to test interaction-effects between CT/MRI variables and between CT/MRI variables and non-stroke-specific vulnerability factors (neuroticism, handicap and positive family history). No significant interaction-effects came out of these analyses.

Discussion

This study has attempted to examine the role of both focal and generalized vascular damage on the incidence of post-stroke depression in a single cohort of 190 first-ever infarct patients who were followed for one year using standardized psychiatric diagnostic scales. Our findings neither support the lesion-location hypothesis, nor the vascular-depression hypothesis as explanatory models for PSD.

As reported previously (Aben *et al.*, 2002a), our study does support, however, the proposition that non-stroke-specific vulnerability factors contribute to the development of PSD. Both the level of neuroticism and handicap came out as independent risk factors, while a positive family history of psychiatric disorders

seemed to further contribute to the risk of PSD. Therefore, in studying the role of biological (stroke-related) factors as independent predictors of PSD these determinants should also be considered. Although in our study we found no evidence of interaction between vulnerability factors and measures of focal or general vascular brain damage, we suggest that more powered studies could reveal such risk-potentiating effects. For instance, vascular white matter lesions may contribute more to a person's vulnerability for depression when the patient has already suffered from depression in the past.

Much to our surprise, an unexpected protective effect of depression was found for infarctions with anterior involvement, when analyzing the overall model with both stroke specific and non-specific factors. This finding opposes the proposed role of damage to the frontal region of the brain in inducing post-stroke or vascular depression and needs further elaboration. A possible explanation for this finding may be sought in the probable under-representation of left frontal strokes by the exclusion of patients with severe aphasia or other severe cognitive deficits from this study. As a consequence, other neurological deficits that are related to posterior brain dysfunction, such as visuo-spatial disturbance or hemi-neglect, may also trigger the development of PSD. As an alternative and more conservative explanation, the finding may be based on a type I statistical error. It must be noted that the significant effect was only found in multivariate (11 factor model and stepwise regression model) and not in bivariate analysis.

A variety of previous studies by others also failed to replicate the lesion-location hypothesis, but Robinson and colleagues carried out a meta-analysis (Narushima *et al.*, 2003) and claimed to have found an interaction between lesion location and time of onset of PSD. Left-hemisphere lesions would increase the risk of PSD, especially in the first few months after stroke, whereas in the chronic course, psychosocial factors would become more important. We tried to test this modification of his original hypothesis by controlling for time-dependency in the Cox regression model but found no such effect. Gainotti had tested this same assumption in 1999 and found that both the symptom profiles and anatomical-clinical correlates of major PSD were not different in the acute and more chronic stages of stroke (Gainotti *et al.*, 1999).

Despite of the negative findings that undermine the plausibility of the lesion-location hypothesis, it cannot be rejected yet. A more precise delineation of specific brain structures that may be involved in mood regulation and, therefore, in the development of PSD, may result in more consistent evidence in favor of the lesion location hypothesis. Vataja *et al.* showed that this strategy seems hopeful, since in their study of 275 stroke patients, they found that infarcts affecting the pre-frontosubcortical circuits, especially the caudate, pallidum, and genu of internal capsule (with left-sided predominance) were associated with a higher prevalence of PSD (Vataja *et al.*, 2001).

Concerning the vascular depression hypothesis, we argue that in a stroke population (pre-stroke) vascular brain damage, as measured by leukoaraiosis and silent cerebral infarctions, does not significantly contribute to the development of PSD, since the direct consequences of stroke itself (either biological, psychological or social) are so strongly depressogenic that the contribution of pre-existing small vascular lesions is overshadowed. In their study, Vataja *et al.* (2001) also failed to find an association between white matter lesions and PSD. This explanation is supported by the recent finding by Mast *et al.* (2004a; 2004b) that in a large cohort of 670 rehabilitation patients, depression was associated with increased burden of cerebrovascular risk factors in patients without stroke but not in stroke patients. It is additionally noted that our group also failed to find a significant contribution of generalized vascular damage to the development of post-stroke cognitive disorders (Rasquin *et al.*, 2004).

The main shortcoming of the study lies in the limited number of available MRI scans, so that we had to rely on CT data in a majority of cases. CT scans made in the acute phase of stroke failed to detect “fresh” infarction of brain tissue in 53 of 114 (46.5%) cases and they are also less sensitive in detecting vascular white matter lesions. Therefore, clinical data were used to complete data on lesion characteristics such as hemisphere involvement and type of stroke (territorial vs. lacunar). Additionally, in pooling CT and MR data, variables were dichotomized in order to reduce the chance of systematic measure errors.

Given the rather equal distribution of strokes over both hemispheres, it is not likely that exclusions have led to essential under-representation of right- or left-hemisphere strokes. Because of the relatively low frequency of infarcts with cortical involvement, of which a minority of 43% were located in the left hemisphere, it seems, however, that cortical strokes have been excluded relatively frequently, especially in the left hemisphere. One can imagine that patients with severe aphasia or generalized cognitive disabilities are especially vulnerable to depression, so that the cumulative incidence of PSD as reported in this thesis may be underestimated. These limitations may have contributed to the negative results of this study.

In conclusion, we found no support for both the lesion-location hypothesis and the vascular-depression hypothesis in stroke patients. In order to appreciate the lesion-location hypothesis for its true value, future research should aim to overcome the methodological difficulties in PSD research such as the exclusion of patients with severe aphasia or other cognitive deficits in our study. Furthermore, a more detailed determination of neuronal circuits that are involved in mood regulation may also prevent the influential hypothesis of Robinson being rejected on immature research findings.

Conflict of interest declaration

None.

Description of authors' roles

I. Aben participated as a PhD student in all phases of the research and wrote the paper. F. Verhey was his primary supervisor throughout; J. Lodder supervised the analysis of the CT and MR imaging and the preparation of the paper, and R. Lousberg was responsible for the statistical design and supervised the statistical analysis. A. Boreas was involved in the recruitment of stroke patients and in the management of the Maastricht Stroke Registry. All authors read, corrected, and approved with the contents of the paper.

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