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DEPRESSION AND EXECUTIVE DYSFUNCTION AFTER STROKE

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ABSTRACT

Background

After ischemic stroke, depression occurs in up to 40% of patients. Even after two decades of intense research, the relationship between lesion characteristics of brain infarcts such as lesion location and post-stroke depression (PSD) is still controversial. Further, executive dysfunction, related to frontal-subcortical circuit dysfunction, has been suggested to be the core defect in patients with geriatric or vascular depression. According to some authors, patients with both depression and executive dysfunction (depression-executive dysfunction syndrome, DES) may form a distinct patient group, with poor functional prognosis and specific treatment options. However, the neuroanatomical correlates of executive dysfunction, or DES, are still not well established.

We wanted to study the magnetic resonance imaging (MRI) correlates of depression and executive dysfunction in stroke patients and to distinguish patients with DES post-stroke by radiological and clinical characteristics. Finally, we wanted to study the impact of PSD on functional outcome at 15 months after stroke. Based on the existing literature, we hypothesized that lesions affecting frontal-subcortical circuitry would be associated with depression and executive dysfunction, and that depression at three months would have an impact on long-term functional outcome after stroke.

Patients and methods

We assessed 486 consecutive patients aged 55 to 85 years three to four months after ischemic stroke. A medical and neurological evaluation was carried out, with several structured instruments for assessment of such factors as activities of daily living (ADL), handicap, depressive symptoms, anxiety symptoms, psychosocial functioning, and stroke severity. A comprehensive psychiatric evaluation included the computer-assisted structured Diagnostic and Statistical Manual of the American Psychiatric Association (the 3rd revised version, and the 4th version, DSM III R and DSM IV, respectively) diagnostics, and several rating scales. A standardized MRI protocol detailed the side, site, type, and extent of brain infarcts, as well as extent of white matter lesions and brain atrophy. Different aspects of executive functions were studied by widely used neuropsychological tests, and a sum score of eight different measures was calculated for each patient to assess the presence of executive dysfunction.

Neuroradiological correlates of PSD were studied in two patient populations. In the first approach, we included all patients with any number of brain infarcts. Of the original 486 patients, the 275 who had undergone both the psychiatric examination and the MRI participated (I). In the second study, we included only those patients who had one and only one brain infarct clinically contributing to the index stroke, plus stroke-related depression as judged by a psychiatrist (total number of patients, 70, Study II).

Both MRI and extensive neuropsychological tests were carried out for 214 patients (Study III) to determine the association between lesion location and executive dysfunction. A psychiatric examination was performed for 158 of these patients (Study IV), and DES was diagnosed in 21. We then studied the radiological and clinical correlates of DES. At 15 months, we assessed functional outcome and its correlates at three months after stroke by different ADL-, cognition- and depression-related scales (Study V).

Results

Patients with depression had a higher number and larger volume of infarcts affecting the prefrontal-subcortical circuits, especially the caudate, the pallidum, and the genu of the internal capsule, with a left-side predominance. The extent of white matter lesions and atrophy did not differ between patients with and without depression (Studies I, II).

The mean frequency of brain infarcts in the left hemisphere was higher in the patients with executive dysfunction.

Lesions affecting the frontal-subcortical circuits (e.g., pallidum, corona radiata or centrum semiovale) were more frequent in patients with executive dysfunction than in those without. Furthermore, patients with pontine brain infarcts frequently had executive dysfunction, but this may have been due to more extensive ischemic changes in these patients in general. Extent of white matter changes and central and medial temporal brain atrophy were also correlates of executive dysfunction (Study III).

The 21 patients with DES had significantly more brain infarcts affecting their frontal-subcortical circuit structures than did the 137 patients without DES, or the 41 patients with depression but without executive dysfunction.

Patients with DES also exhibited more severe depressive symptoms and worse psychosocial functioning, and coped less well with complex activities of daily living (Study IV).

Major depression or depression as defined by the BDI (Beck's Depression Inventory) cutpoint of ≥10 were associated with poor functional outcome at 15 months.

Likewise, major depression at three months was associated with a worse outcome or dependence in ADL functions (Study V).

Conclusions

The location of the brain infarct was a determinant of PSD, executive dysfunction, and DES. The controversy in the literature regarding lesion location and PSD is probably the result of methodological problems, e.g., weakness of computer tomography in infarct characterization and inadequate diagnostic assessment of depression. Further MRI-based studies in lesion location will be needed to confirm our pioneering results. Our results also support the novel hypothesis of frontal-subcortical circuits as regulators of mood and emotion. Finally, PSD at three months was also an important determinant of functional outcome at 15 months after stroke.

LIST OF ORIGINAL STUDIES

I. Vataja R, Pohjasvaara T, Leppävuori A, Mäntylä R, Salonen O, Aronen H, Kaste M, Erkinjuntti T. MRI correlates of depression after ischemic stroke. ArchGen Psychiatry 2001; 58:925-31.

II. Vataja R, Pohjasvaara T, Leppävuori A, Mäntylä R, Salonen O, Aronen H, Kaste M, Erkinjuntti T. Post-stroke depression and lesion location revisited. J Neuropsychiatry Clin Neurosci 2004; 16: 156-62.

III. Vataja R, Pohjasvaara T, Mäntylä R, Ylikoski R, Leppävuori A, Leskelä M, Kalska H, Hietanen M, Aronen HJ, Salonen O, Kaste M, Erkinjuntti T. MRI correlates of executive dysfunction in patients with ischaemic stroke. Eur J Neurol 2003;10:625-31.

IV. Vataja R, Pohjasvaara T, Mäntylä R, Ylikoski R, Leppävuori A, Leskelä M, Kalska H, Hietanen M, Aronen HJ, Salonen O, Kaste M, Erkinjuntti T.Depression -executive dysfunction syndrome in stroke patients. Am J Geriatr Psychiatry 2005;13:99-107.

V. Pohjasvaara T, Vataja R, Leppävuori A, Kaste M. Erkinjuntti T. Depression is an independent predictor of poor long-term functional outcome poststroke. Eur J Neurol 2001;8:315-9.

ABBREVIATIONS

ACA	Anterior cerebral artery
ADL	Activities of daily living
APA	American Psychiatric Association
BDI	Beck's Depression Inventory
BI	Barthel Index
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical strokes and vascular dementia
CT	Computed tomography
CVD	Cerebrovascular disease
DES	Depression-executive dysfunction syndrome
DSM III	Diagnostic and Statistical Manual of the American Psychiatric As-Association, 3rd version
DSM III R	Diagnostic and Statistical Manual of the American Psychiatric Association, 3rd revised version
DSM IV	Diagnostic and Statistical Manual of the American Psychiatric Association, 4th version
ECT	Electroconvulsive therapy
FAQ	Functional Activities Questionnaire
GAF	General Assessment of Functioning Scale
IADL	Instumental activities of daily living
ICH	Intracerebral hemorrhage
MADRS	Montgomery-Åsberg Depression Rating Scale
MCA	Middle cerebral artery
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NINDS	National Institute of Neurological Disorders and Stroke
OR	Odds ratio
PCA	Posterior cerebral artery
PSD	Post-stroke depression
PSE	Present State Examination
RS	Rankin Scale
SAM	Stroke Aging Memory Study
SAS	Zung Anxiety Score
SAV	Subarachnoid haemorrhage
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SD	Standard deviation
SSRI	Serotonin-selective reuptake inhibitor

SSS	Scandinavian Stroke Scale
TIA	Transient ischemic attack
WMC	White matter change

INTRODUCTION

This work concerns cerebrovascular disease (CVD), depression, frontal cognitive functions, and the complex interactions of all three. Both depression and CVD are, in this era of aging populations, receiving increasing attention. CVD is the second most important cause of death world-wide (Murray and Lopez, 1997), and incidence of stroke increases with age. Thus, overall age- and sex – standardized incidence rates of stroke in Europe are 9 per 1000 person-years for individuals of ages 65 to 84, and 17 for those over 75 years (Di Carlo et al., 2000). Although in Finland the mortality and age-adjusted incidence of stroke are decreasing (Sivenius, 2004), the absolute number of patients is probably increasing due to the elderly population's extended life expectancy and increasing size.

Stroke is caused by ischemic brain infarct in 80% of all cases, with transient ischemic attacks and intracerebral and subarachnoidal hemorrhages being less frequent (Bonita, 1992). The consequences of stroke are often catastrophic for the patient, and a significant economic burden for society in the form of loss of ability to work, loss of independence in ADL, and nursing home placement (Kaste et al., 1998).

Depression and other neuropsychiatric aspects of stroke are still too often neglected in clinical practice. In the scientific community, the importance of post-stroke depression (PSD) has however been acknowledged, with new papers appearing in 2004 in journals registered in the MEDLINE database numbering 50 to 60. Stroke survivors are at greatly elevated risk for clinically significant depressive symptoms even years after stroke, independent of functional disability or previous depressive symptoms (Whyte et al., 2004). PSD is also an important and independent correlate of poor functional outcome (Herrmann et al., 1998) and mortality (Morris et al., 1993). Further, in stroke patients, quality of life is seriously affected, and the most important factor causing this change is PSD (Kauhanen, 1999). Both the human and economic burden associated with stroke could thus be diminished by effective prevention or management of PSD (Hachinski, 1999).

Theoretically, PSD provides a valuable model for understanding the neurobiology and disturbances of mood regulation in general. Depression as a consequence of localized brain damage helps identifying critical cerebral structures and connections as well as neurochemical changes that may be involved in functional depression.

Because both depression and frontal cognitive symptoms like executive dysfunction are probably mediated by dysfunction in adjacent and overlapping frontal neural systems and circuits (Cummings, 1993), patients with depression also often show executive dysfunction (Royall, 1999). The frontal executive deficits, rather than disturbance of mood or affect, may explain depressed patients'disability. These possible associations are clinically important, as more specific treatment of these cognitive aspects of depression may help to ensure functional recovery.

In the present study we examined the pathoanatomical MRI correlates of both PSD and executive dysfunction. Understanding the mechanisms and characteristics of these disorders may help in identifying these patients more readily in the future for either already existing or emerging novel and more specific treatments.

REVIEW OF THE LITERATURE

Concept of vascular depression

1. Depression in patients with vascular disease

The relationship between vascular disease and depression is complex and bi-directional. Thus, a growing body of evidence suggests that vascular diseases increase risk for subsequent depression. On the other hand, depression is a risk factor for subsequent vascular disease and stroke.

The reported prevalence of depression in elderly people varies among studies. In community-based studies using DSM III and IV criteria, the prevalence of major depression is about 3 to 5% and that of minor depression usually two to four times higher (Kivelä, 2002, Gallo and Lebowitz, 1999). In a recent US population-based study focusing on the general elderly population aged 65 to 100 (Steffens et al., 2000), the point prevalence of major depression among the non-demented was estimated to be 4.4% for women and 2.7% for men. In Finland, a lower prevalence of major depression has emerged from the Health 2000 Study, being 1.1% for males and 2.7% for females (Pirkola et al., 2005).

In patient populations the prevalence is higher. Elderly patients in general practice are probably more affected, and the prevalence of "clinically significant" depression (defined by rating-scale cut-points) has been between 17 and 30% (Callahan et al., 1994, Evans and Katona, 1993). In patients with vascular diseases, however, major depression is even more prevalent. For example, of inpatients recovering from heart infarct around 20% may suffer from major depression (Hance et al., 1996, Frasure-Smith et al., 1993).

Depression is probably a more common feature of vascular dementia than of Alzheimer's disease (Newman, 1999). Silent (causing no neurological symptoms) brain infarcts are significantly more common in elderly depressed patients than in non-depressed subjects (Fujikawa et al., 1993). This association is even clearer in those patients with late-onset depression and without a family history of or with fewer psychosocial risk factors for depression (Fujikawa et al., 1997).

The relationship between cerebrovascular risk factors (hypertension, smoking, coronary artery disease, diabetes mellitus) and depression is less clear, however, as most of the data come from cross-sectional studies from which directionality cannot be established (Lyness, 2002, Tiemeier et al., 2004). Two recent follow-up studies have approached this subject. In the study by Lyness

et al. (2000), severity of a cumulative cerebrovascular risk factor index associates significantly independently with one years depressive diagnoses–but not after controlling for overall medical burden. Mast et al. (2004), on the other hand, found that after controlling for baseline levels of depression, general medical burden, limitations in activities of daily living, cognitive impairment, and demographic variables including age, education, gender, and race, baseline vascular burden was associated with increased odds for depression at 6- and 18-month follow-up assessments (Mast et al., 2004). Thus, vascular risk factors may also prove to be risk factors for old-age depression.

The largest body of evidence for an association between cerebrovascular disease – in the absence of frank brain infarcts – and depression comes from neuroradiological studies. White matter and deep gray matter (i.e., basal ganglia) hyperintensities have been repeatedly reported as more common in patients with late-life depression (O'Brien et al., 1996, Steffens et al., 1999, de Groot et al., 2000). Such intensities may in general be caused by unspecific demyelination or gliosis. However, neuropathological studies have shown that in elderly depressed patients, white matter changes (WMC) detected in magnetic resonance imaging are of vascular origin, especially in the frontal dorsolateral white matter of the brain (Thomas et al.,2002 a, 2002 b). Further, left-sided white matter lesions seem to be more common in patients with late-onset depression, suggesting lateralized lesion involvement in the pathophysiology of depression even when brain infarcts are absent (Tupler et al., 2002). In the periventricular white matter of depressed patients, causes of hyperintensities are more heterogenous, but larger hyperintensities are probably markers for cerebrovascular disease (Thomas et al., 2003a).

The idea of vascular disease as causative or as a risk factor for depression has been widely recognized. However, even stronger evidence links previous depression and subsequent vascular disease. Many large prospective studies have shown that depression is an independent risk factor for later developing cardiovascular disease or myocardial infarct (Thomas et al., 2004). A study by Pratt et al (1996) suggests a dose-effect: Previous major depression has a stronger impact as a subsequent risk factor for coronary artery disease than does dysthymia.

Similarly, patients with depression have had an increased risk for stroke in follow-up studies (Larson et al., 2001, Jonas and Mussolino, 2000). Longstanding depression in elderly people also leads to increased mortality (Pulska et al., 1999); this may in part be explained by excess stroke mortality in depressive patients. Previous depression increases stroke-associated mortality even more than do classical risk factors like smoking or high cholesterol levels (Gump et al., 2004).

The pathophysiological mechanisms linking depression and subsequent CVD are unknown. Depressive elderly subjects with chronic medical illnesses are less compliant with medical treatment regimens, and their poor adherence may explain their increased risk for vascular morbidity (Carney et al., 1995). Other mechanisms proposed include effects of hypercortisolemia, platelet hyperaggregation causing thrombosis, immunoactivation, or abnormal homocysteine metabolism (Kales et al., 2005, Tolmunen et al., 2004).

2. Vascular depression

The many lines of evidence here presented have led some authors to propose a novel hypothesis of vascular depression, a late-onset form of depression in patients with established cerebrovascular disease and/or risk factors (Alexopoulos et al., 1997a, Alexopoulos et al., 1997b, Krishnan et al., 1997), (Table 1).

Table 1. Proposed criteria for vascular depression (Krishnan et al., 1997) with Criteria A and either B1, B2, or B3 present

A. Major depression occurring in the context of clinical and/or neuroimaging evidence of cerebrovascular disease or neuropsychological impairment
B1. Clinical manifestations of cerebrovascular disease such as history of stroke or focal neurological findings)
B2. Neuroimaging findings such as white or gray matter hyperintensities, confluent white matter lesions, or brain infarcts
B3. Cognitive impairment manifested by executive dysfunction
The diagnosis may be supported by 1) Depression onset after age 50 2) Marked loss of interest or pleasure 3) Psychomotor retardation 4) Lack of family history of mood disorders 5) Marked disability in activities of daily living

The characteristic features of vascular depression have been suggested to include reduced depressive ideation, psychomotor retardation, apathy, executive dysfunction, and delusional symptoms (Baldwin and O'Brien, 2002, O'Brien et al., 1997), but some studies have failed to find differences between the symptoms of depressive elderly patients with and without vascular disease (Licht-Strunk et al., 2004). Thus far, no consensus exists as to whether major depression criteria should be required, and how the criteria for cerebrovascular disease should be described (e.g., disease severity thresholds) (Steffens, 2004).

3. Other vascular-related behavioral syndromes

The concept of vascular depression has been largely adopted and adapted from that of vascular dementia, and the continuing evolution of the vascular dementia paradigm also affects the way we think about neuropsychiatric consequences of cerebrovascular disease. The DSM IV criteria for vascular dementia describe an Alzheimers' -like, memory-focused cognitive disorder, judged to be caused by cerebrovascular disease of which either clinical or neuroradiological evidence is required (American Psychiatric Association, APA; 1994). However, the term vascular dementia is currently being replaced by a broader and a more relevant concept of vascular cognitive impairment. This term covers a range of distinct vascular disorders leading to cognitive impairment, i.e., multi-infarct dementia, post-stroke dementia, subcortical vascular dementia, mild cognitive impairment, and hereditary vascular disorders leading to cognitive decline (O'Brien et al., 2003). It also recognizes the role of vascular factors in degenerative dementias like Alzheimer's disease (Snowdon et al., 1997)

The association between vascular depression and vascular cognitive impairment is probably strong. They share the same risk factors, and at least some of the pathophysiological mechanisms are similar, e.g., disruption of frontal-subcortical circuitry (Cummings, 1993). Patients with vascular depression often have cognitive symptoms, most notably executive function, which is also a hallmark of cognitive decline in vascular cognitive impairment (Erkinjuntti et al., 2000a). It is therefore possible that vascular depression precedes vascular dementia (Steffens et al., 2003), and that vascular depression may be a warning sign for imminent development of dementia. However, no studies have directly addressed this potentially clinically important relationship.

Increased white matter intensities have also been shown in patients with bipolar disease, especially in the elderly patients (Aylward et al., 1994), and these changes are associated with poor outcome (Moore et al., 2001). However, no evidence of any vascular origin of white matter changes in bipolar patients yet exists.

Another important syndrome in the context of cerebrovascular disease, cognitive impairment, and neuropsychiatric symptoms is cerebral autosomal dominant arteriopathy with subcortical strokes and vascular dementia (CADASIL). Patients with CADASIL typically present with transient ischemic attack (TIA) or stroke; cognitive impairment like executive dysfunction, apathy, or full-blown vascular dementia are present in 60% of symptomatic patients. (Dichgans et al., 1998). Neuropsychiatric symptoms like major depression, bipolar disorder, or delusions occur in 30% of these cases (Dichgans, 2002). Subcortical periventricular white matter changes and lacunar infarcts in the basal ganglia and

thalamus are typical neuropathological findings in these patients, again suggesting the disruption of frontal-subcortical circuitry as a pathophysiological mechanism for neuropsychiatric symptoms in cerebrovascular diseases.

Vascular depression and cognition

1. Frontal-subcortical circuits

Five differing frontal-subcortical circuits have been recognized, three of which are associated in man with emotional and cognitive processes in man (Alexander and Crutcher, 1990, Cummings, 1993). These three circuits are designated according to site of origin in the prefrontal cortex, *the dorsolateral prefrontal circuit* (originating from the convexity of the frontal lobe, Broadmann's areas 9 and 10), *the lateral orbitofrontal circuit* (originating from the lower lateral parts of the prefrontal cortex, Broadmann's area 10), and *the anterior cingulate circuit* (originating from the medially located cingular cortex: Broadmann's area 24). From their anatomically diverse areas of origin these circuits run closely adjacent to each other, although segregated, within the subcortical structures of the caudate, globus pallidus, substantia nigra, thalamic nuclei, and interconnecting white matter structures, e.g., the capsula interna and corona radiata, before returning to the frontal cortex; thus forming a closed circuit (Burruss et al., 2000). These circuits also have rich connections with the structures of the limbic circuitry, e.g., amygdala and hippocampus.

Damage to distinct circuits causes specific neuropsychological and neuropsychiatric symptoms (Tekin and Cummings, 2002) Thus, damage to the dorsolateral prefrontal circuit has been associated with cognitive changes, especially dysexecutive function; the orbitofrontal-subcortical circuit with irritability and agitation; and the anterior cingular circuit with apathy. The circuits run closely adjacent to each other after leaving the prefrontal cortex, and therefore are likely together to suffer damage caused by subcortical brain infarcts. The resulting clinical picture is a variable mixture of cognitive and psychiatric symptoms **(Table 2)**. Depression has mostly been connected with orbitofrontal and anterior cingular dysfunction (Ballmaier et al., 2004, Mayberg, 2001). The association of PSD with other syndromes like apathy (Starkstein et al., 1993) and dysexecutive function (Leeds et al., 2001, Kauhanen et al., 1999) is understandable in the context of the frontal-subcortical circuitry model.

Table 2. Neuropsychiatric symptoms and syndromes associated with dysfunction of frontal-subcortical circuits (McPherson, 1998)

Dorsolateral circuits	Orbitofrontal circuits	Anterior cingular circuits
Executive dysfunction	Personality change	Apathy
Working memory disturbances	Poor judgement	Abulia
Motor planning and sequencing disturbances	Irritability	Akinetic mutism
	Hypomania and mania	Amotivation
	Impulsivity	Depression
	Depression	

2. Executive dysfunction in patients with cerebrovascular disease

Executive functions are high-order cognitive processes necessary for complex, goal-oriented behavior. They include control and regulation of behavior and are critical for novel problem-solving (Rabbitt, 1997). The APA's Diagnostic and Statistical Manual, 4th Edition (DSM IV) (APA, 1994) defines executive functions as the ability to think abstractly and to plan, initiate, sequence, monitor, and cease complex behavior; to shift mental sets, generate novel verbal or non-verbal information, and to execute serial motor activities. Thus, executive functions are often viewed as distinct cognitive functions directly measurable by neuropsychological testing.

A more cybernetic approach to executive functions is also emerging (Royall et al., 2002). Here executive functions are seen as central controlling functions, interacting, sequencing, and organizing non-executive processes as well (e.g., motor, emotional, and sensory processes). Executive dysfunction could also express itself as disorganized operations of non-executive domains, such as hallucinations in patients with schizophrenia (Andreasen et al., 1998).

Executive dysfunction is probably one of the central defects (Royall et al., 2002) in a wide spectrum of neuropsychiatric disorders like schizophrenia (Pantelis et al., 1997), traumatic brain injury (Hanks et al., 1999), late-onset depression (Alexopoulos et al., 2002), or vascular dementia (Roman and Royall, 1999). It compromises coping in non-routine tasks and complex ADLs (Grigsby et al., 1993), thus endangering independent functioning and increasing institutionalization of patients with chronic neuropsychiatric conditions.

Lesions affecting the dorsolateral prefrontal cortex cause executive dysfunction (Grafman and Litvan, 1999), but damage to the frontal-subcortical circuits

and their thalamocerebellar connections may have similar effects also in subcortical (Cummings, 1995, Kramer et al., 2002) and posterior (Schmahmann and Sherman, 1998) areas. In healthy individuals, executive dysfunction has been associated with the volume of WMCs assessed by MRI (DeCarli et al., 1995). Clinically significant executive dysfunction is also a frequent consequence of ischemic stroke, associating with dementia and disability (Pohjasvaara et al., 2002a). The few existing case studies or patient series reporting anatomic location of the brain infarcts in stroke patients (Caplan et al., 1990, Ghika-Schmid and Bogousslavsky, 2000, Sandson et al., 1991, Van Der Werf et al., 1999, Wolfe et al., 1990, Mangels et al., 1996) highlight the significance of dorsolateral frontal, thalamic, or caudate infarcts for executive dysfunction. However, in clinical practice, dysexecutive function is often found in patients with brain infarcts affecting other regions of the brain, such as cerebellum.

3. Depression-executive dysfunction syndrome (DES)

Late-life depression is a heterogeneous disorder that mainly occurs in relation to poor medical health and brain lesions, often of vascular origin (Alexopoulos et al., 1997a). It is therefore not surprising that these patients often show defects in cognitive functioning. A typical feature of late-life depression is a significant impairment in executive functions (Lockwood et al., 2002). This is clinically significant, since in patients with geriatric depression executive dysfunction is associated with compromised instrumental activities of daily living (IADL) (Kiosses et al., 2000, Lockwood et al., 2002), leading to increased risk for relapse and for recurrence of depression (Alexopoulos et al., 2000), and to poor response to antidepressant treatment (Kalayam and Alexopoulos, 1999). Alexopoulos (2001) has suggested that, in a significant subgroup of patients with late-life depression, depressive symptoms, and executive dysfunction result from related frontostriatal dysfunction. These patients with the DES would be characterized by psychomotor retardation and reduced interest in activities, but with a less pronounced vegetative syndrome than that of those elderly depressed patients without significant executive dysfunction (Alexopoulos et al., 1996). Targeted studies of novel pharmacological agents known to modulate the frontostriatal functions, e.g., opiate agonists, dopamine agonists, and cholinergic agents, might prove useful in this specific group of depression patients (Alexopoulos et al., 2002)

Post-stroke depression

1. Prevalence of post-stroke depression (PSD)

Folstein et al reported in 1977 that when they compared 20 stroke patients with 10 orthopedic patients with equally compromised activities of daily living (ADL), depression occurred in 45% of the stroke patients, but among orthopedic patients, in only 10%. This is, thus far, the only study with such a direct comparison between patients with stroke and with other chronic disorders.

Numerous studies have addressed the prevalence of depression in stroke patients, with percentages varying from study to study, depending on time elapsed between onset of stroke symptoms, study setting (acute inpatient vs. rehabilitation phase, hospital vs. outpatient), and diagnostic criteria. Some of the essential studies reporting prevalence rates of post-stroke depression are presented in Table 3. The estimated prevalence of depressive disorders has been around 20% to 40 %. In one recent study comparing one-year cumulative incidence of minor and major depression between patients with ischemic stroke and myocardial infarct, incidence of depression was higher in patients with stroke (38% vs. 25%), but this difference was not significant after controlling for sex, age, and handicap (Aben et al., 2003).

Depression is also common in other disorders that directly affect the brain. Major depression was present in 27% of patients referred to general neurology outpatient clinics for any reason (Carson et al., 2000b). In Parkinson's disease (Cummings, 1992), multiple sclerosis (Ron and Logsdail, 1989), and in outpatients with traumatic brain injury (Kreutzer et al., 2001), prevalence of depression has been around 40%.

In conclusion, although comparisons of reported prevalence from different patient populations are difficult, depression is clearly more prevalent in post-stroke patients than in the general elderly population, and possibly also more prevalent than in patients with myocardial infarct. In patients with Parkinson's disease, multiple sclerosis, or traumatic brain injury, the reported prevalence of depression equals that of PSD. This indirect evidence suggests that brain injury *per se* may elevate the risk for depression, in addition to the psychosocial stress caused by severe disease.

Table 3. Studies of prevalence and significance of lesion location in post-stroke depression

Source	N	Setting	Prevalence of depression (%)	Association between lesion location and depression	Depression criteria	Time from stroke to assessment
Robinson et al., 1984	36	Inpatient	44	Left side more common	DSM III Major and minor depression	Acute
Sinyor et al, 1986	35	Rehab	40	Right side more common	Major and minor depression	2 weeks
Starkstein et al., 1987	45	Inpatient, rehab	31	Left side more common	DSM III Major and minor	Mean, 20 days
Dam et al., 2001	92	Inpatient, outpatient	30	No difference	Research diagnostic criteria (RDC)	Mean, 35 days
Sharpe et al., 1990	60	Community	18	No difference	Any DSM-III-R depression	3 to 5 years
House et al., 1989b	73	Community	11 (one month) to 5 (12 months)	No difference	DSM III Major	1, 6, and 12 months after stroke
Schwartz et al., 1993	91	Rehab	40	Right side more affected in depression	Major and minor depression	3-9 months
Åström M et al., 1996	80	Inpatients	25 (acute stage), 31 (3 months), 16 (12 months), 29 (3 years)	Left anterior lesion more common in acute stage, not later	DSM III major depression	Acute phase-3 years
Herrmann M et al., 1995	47	Inpatients	36	Left basal ganglia lesions were correlated to depression	Any DSM-III-R depression	<2 months
Andersen et al., 1995	285	Inpatient, outpatient	30	No difference	Major depression	1 month
MacHal et al., 1998	145	Inpatient	20	Right hemisphere more common	DSM IV major and minor	6 months
Gainotti et al., 1999	153	Inpatients, rehab	27 (<4 months) 40 (>4 months)	No difference	DSM III R Major depression	2 weeks to 6 months
Kim and Choi-Kwon, 2000	148	Outpatients	18	No differences between hemispheres, anterior more common than posterior	DSM IV major depression	2-4 months

2. Relationship between lesion location and PSD

The association between location of brain damage and subsequent changes in behavior has been demonstrated in classic neuropsychology, i.e., in aphasic or amnestic disorders. Current knowledge in neurobiology emphasizes the model of wide-distributed neural networks, rather than strictly localized brain areas as the anatomical basis of distinct complex brain functions. However, there may exist some critical "relay areas" or areas of anatomical proximity of different neural networks that, when damaged, may give rise to disturbances in behavior or affect.

PSD is an important subtype of vascular depression. In vascular depression, the disruption in the mood-regulating circuits may be caused by white-matter changes, whereas in post-stroke depression, brain infarct or hemorrhage causes this disruption. The significance of frontal-subcortical structures in depression is evident also from both structural (Soares and Mann, 1997) and functional (Drevets, 2000) studies of endogenous, "non-organic" depression. Abnormal findings are repeatedly reported in the prefrontal cortex, striatum, and thalamus; but also in the classical limbic structures, especially the amygdala.

Robinson and colleagues from the University of Iowa, USA, were the first to focus on laterialization of behavioral and biochemical responses after cerebral infarction, using an experimental stroke model. They showed that spontaneous activity increased in association with decrease in norepinephrine concentrations in rats with right-sided lesions, whereas no biochemical or behavioral changes were noted in rats with left-sided lesions (Robinson et al., 1975, Robinson, 1979). Their further studies concentrated on the relationship between lesion location and depression after brain injury in humans (Robinson and Szetela, 1981). They showed that depression, as well as severity of depressive symptoms, was associated with the anteriority on computed tomography (CT) of the brain lesion. Further, left-sided lesions, particularly left anterior lesions, were associated with PSD (Robinson et al., 1983b, 1984, Starkstein et al., 1987)

After the seminal work by the Robinson group, more than fifty studies have appeared addressing the correlation between stroke lesion location and depression. The most prominent studies are presented in Table 3. Starkstein et al. (1988) first showed that patients with left-sided basal ganglia lesions more frequently had more frequent depression than did patients with right–sided or thalamic lesions; depressive symptoms were also more severe in association with left-sided basal ganglia lesions. Since then, many studies have consistently shown that lesions affecting basal ganglia and frontal structures associate with PSD (Morris et al. 1996, Kim and Choi-Kwon, 2000).

Virtually all studies of lesion location and PSD have applied CT methodology in characterizing the stroke lesion and its location, and most have recruited only patients with a single stroke lesion. The results of the many studies in this field are conflicting: some report no association with lesion location and depression; some find associations with right-sided lesions and depression. Robinson (1998a) has suggested that the relationship between PSD and lesion location is dynamic, so that the association exists in the acute phase after stroke but not in later stages, i.e., three months after stroke. This explanation is in accordance with findings of some follow-up studies (Shimoda and Robinson, 1999, Åstrom et al., 1993). However, Carson et al (2000) have argued strongly against the "left anterior hypothesis" in their systematic review of the existing studies in this field. Their fixed-effects and random-effects meta-analysis of the pooled data from 48 studies found no evidence for the lesions of the left hemisphere or of the left anterior brain being critical in PSD. This meta-analysis has in turn been criticized for not taking into account past psychiatric history, prior brain injury, or subcortical atrophy – all potentially important contributors to the association between brain infarct and subsequent depression (Whyte and Mulsant, 2002).

All in all, the association between stroke lesion location and depression, and indeed the concept of post-stroke depression as a biological vs. psychosocial form of depression is still controversial. This field is plagued by a high number of studies using different and in part contradicting methodologies and definitions and thereby reaching confusing results. To clarify matters, many authors have suggested standardization of the protocols in future PSD studies (Singh et al., 1998, Bhogal et al., 2004, Turner-Stokes, 2003, Aben et al., 2003). Among the key problems still to be resolved are

- Lack of standardized and appropriate measure for depression in stroke patients, i.e., patients with communicative problems like aphasia, neuropsychological problems like neglect, or neuropsychiatric symptoms like apathy or fatigue not necessarily caused by depression
- Identification of a representative population source; i.e., hospital-based vs. outpatient setting
- Optimal time after stroke outset to interview for PSD; a prospective follow-up study should probably be preferred to cross-cut studies
- Ideal neuroradiological assessment; probably a blinded protocol with specified methods for brain infarct identification, assessment of brain atrophy, and white matter changes
- Significance of various host factors, i.e., social support, disability after stroke, pre-stroke depressive episodes, family history of depression, or medications

3. Other possible pathophysiological mechanisms of PSD

Neurotransmitter changes contributing to development of PSD are unclear. Studies of receptor binding in animal models and human patients as well as fenfluramine challenge studies (to measure the effect of fenfluramine-induced serotonin increase on serum prolactine levels) suggest that disturbances in the metabolism of dopamine, serotonin and norepinephrine may be involved (Robinson, 1998a, Ramasubbu et al., 1998a).

Theoretically, stroke-associated deleterious neuroplastic changes may also affect mood and increase risk for PSD. Neuronal damage may lead to impairments in signaling pathways that regulate neuroplasticity and cell survival. The resulting decreased expression of brain-derived neurotrophic factors in populations of stress-vulnerable hippocampal neurons may be involved in depression. (Duman et al., 1997, Manji et al., 2001).

Although biological explanations for PSD are, however, intriguing, like any other psychiatric condition, it is a multidimensional disorder with biological and psychosocial aspects. Among reported risk factors for PSD are premorbid neurotic personality (Aben et al., 2002), family history of depressive disorders, and previous depressive episodes (Morris et al., 1992). Furthermore, major life events other than stroke (Bush, 1999), living alone before stroke, female gender, social stress before stroke (Andersen et al., 1995), and stroke severity and disability after stroke (Pohjasvaara et al., 1998b) are associated with PSD. Thus, the psychosocial factors should not be forgotten in the clinical practice or in research on this disorder.

4. Treatment of post-stroke depression

The biology behind endogenous and post-stroke depression probably differs, the latter occurring as a result of acute brain damage in contrast with the less robust brain dysfunction of endogenous depression. Therefore, the treatment algorithms for endogenous depression may not necessarily be applicable to PSD. At present, eight controlled studies address this question, in addition to open-label studies. Among the compounds studied are fluoxetine (Wiart et al., 2000, Fruehwald et al., 2003), citalopram (Andersen et al., 1994), nortriptyline (Lipsey et al., 1984, Robinson et al., 2000), trazodone (Reding et al., 1986), reboxetine (Rampello et al., 2004), and methylphenidate (Grade et al., 1998). Data from these studies suggest that PSD does respond to antidepressants with their differing modes of action at a rate comparable to that of endogenous depression. No serious adverse effects occurred in any of these studies. Finally, a recent Cochrane review found evidence of reduction in depression rating scales but no evidence of increased total remission associated with antidepres-

sive medication after stroke (Hackett et al., 2004). This is an understudied field, however, and clinical experience encourages us to avoid nihilism in biological treatment of PSD.

What is the drug of choice for PSD? A trial by Robinson et al (2000) showed that for treatment of PSD, nortriptyline, a tricyclic compound, is superior to fluoxetine and to placebo. Theirs is the only post-stroke depression study thus far with a head-to-head comparison between two compounds. However, anticholinergic (e.g., glaucoma, urine retention, and cognitive deterioration) and potential cardiotoxic effects of nortriptylene clearly limit its usefulness in elderly patients with cerebrovascular disease. Sertraline has been proven safe and effective for depression after myocardial infarct (Glassman et al., 2002), suggesting a favorable safety profile for that drug also in other serious vascular disorders like stroke. As a group, the selective serotonin reuptake inhibitors (the SSRIs) probably have fewer side effects and contraindications in post-stroke patients than do tricyclic antidepressants and are more feasible to use (Cole et al., 2001). Novel agents like mirtazapine, venlafaxine, and reboxetine seem to be safe and effective for PSD in our clinical experience, supported by some open-label trial data (Dahmen et al., 1999).

Electroconvulsive therapy (ECT) is probably also safe and effective for PSD (Currier et al., 1992). Although case reports (Weintraub and Lippmann, 2000) show ECT to be safe even in the postacute phase (7 to 14 days after stroke), it is probably advisable to wait few weeks before ECT to avoid ischemic complications (Miller and Isenberg, 1998).

0Although no controlled trials of different psychotherapeutic approaches in patients with PSD exist, the value of supportive psychotherapy, psychoeducation, and family support in clinical practice is hard to deny. Of the more structured therapy modalities, cognitive psychotherapy is probably worthy of consideration in patients retaining communicative and cognitive skills (Kneebone and Dunmore, 2000, Lincoln et al., 1997).

5. Prognosis of post-stroke depression

Several studies have shown that depression has a deleterious effect on prognosis after stroke. Thus, in one prospective study of 63 stroke patients, the 25 patients with PSD did not differ from those without PSD during acute hospitalization in regards to impairment in ADLs, neurologic diagnoses and findings, lesion location and volume on CT, demographic variables, cognitive impairment, or social functioning. However, at two years after stroke those patients with either minor or major PSD were significantly more impaired in ADLs than were the others (Parikh et al., 1990). Numerous other studies have reported associations between functional disability and PSD, but it has been difficult to con-

clude whether PSD has influenced disability or vice versa (Åström et al., 1993, Ramasubbu et al., 1998b, Singh et al., 2000). The negative effect of depression on functional outcome has also been shown in rehabilitation studies post stroke. Patients with PSD spend a longer time in rehabilitation programs, and their use of rehabilitation services is less efficient (Gillen et al., 2001). Thus, the effect of rehabilitation on recovery from stroke is clearly and negatively affected by PSD (Paolucci et al., 2001).

Cognitive decline as measured by decrease in Mini-Mental State Examination (MMSE) score in association with PSD has often been reported in many studies (Robinson, 1998c), but the proportion of patients with PSD developing dementia within certain time periods, say within a year after stroke, is unknown.

Depression also affects stroke patients' quality of life. In many studies, PSD has been called one of the most important correlates of post-stroke quality of life, in addition to functional disability, family and social support, and subcortical stroke lesion location (Jaracz and Kozubski, 2003, Kauhanen et al., 2000, Carod-Artal et al., 2000, Moon et al., 2004).

Mortality after stroke in patients with depression is significantly higher. Morris et al. (1993) followed 91 stroke patients for 10 years and found that those patients with either minor or major depression at two weeks after stroke were 3.4 times as likely than non-depressed subjects to have died during that time. Similar findings have recently been reported from a large, register-based study of 51,119 American veterans, each hospitalized after an ischemic stroke. The hazard ratio of death within three years after stroke was 1.13 (CI=1.06-1.21) for patients with depression, despite their being younger and having fewer chronic conditions (Williams et al., 2004).

Recently, trials of antidepressive medications to prevent these adverse outcomes in stroke patients have been carried out. Narushima and Robinson (2003) found that a three-month course of antidepressive medication in stroke patients with and without depression was effective in reducing functional impairment at 21 months after stroke, but there seemed to be a time-window: The medication was significantly more effective in prevention of disability when introduced early, during the first month post-stroke, rather than later introduction of medication. In a controlled trial of mianserin for prevention of PSD, however, antidepressive medical treatment failed to affect stroke outcome (Palomäki et al., 1999). Jorge et al. (2003) randomly assigned 104 patients to receive a 12–week double-blind course of nortriptyline, fluoxetine, or placebo during the first six months after stroke. They found significantly more patients of the treatment group (68% vs. 36%) to be alive at 9-year follow up. Thus, antidepressive medication may

improve functional outcome and survival in patients with ischemic stroke, with and without depression.

Post-stroke depression has a negative impact on many aspects life after stroke, but what is the prognosis and natural course of the PSD itself? Robert Robinson et al. (1998b), in a number of papers addressing this matter, suggest that in at least half these patients, the depression tends to last for at least eight months. However, in most cases, the patients improve even without treatment, and remission rates are similar to those in endogenous depression. Thus, at one year after depression, 75% percent of the patients were in remission. While this mostly favorable prognosis is reported also in other studies (Burvill et al., 1995, Morris et al., 1990), a study by Åström et al (1993) suggests that 40% of patients with early (onset at 0 to three months after stroke) major depression were not in remission at one year after stroke, and had a high risk for chronic depression. To sum up, the long-term prognosis for PSD is still an open question, with further studies in this field needed.

AIMS OF THE STUDY

Our basic hypotheses were that location of brain infarcts and other vascular-related brain lesions are associated with depression and executive dysfunction, and that PSD is associated with a worse outcome at one year in stroke patients.

- To study the neuroradiological correlates of post-stroke depression by use of MRI. Based on the existing literature, we expected to find that lesions of frontal-subcortical circuitry would increase risk for PSD (Studies I and II).
- To evaluate the association between lesion location and executive dysfunction in stroke patients. As frontal control of executive functions and mood may be mediated by closely adjacent frontal-subcortical circuits, we expected to find that lesions of frontal-subcortical circuits would also be associated with executive dysfunction (Study III).
- To discover whether lesion locations would differ between patients with and without depression, with and without executive dysfunction. We hypothesized that in patients with both depression and executive dysfunction, frontal-subcortical lesions would be especially common. We also sought other correlates for this clinically potentially important patient group of DES (Study IV).
- Finally, we wanted to highlight the significance of PSD the outcome after stroke by assessing the correlation between depressive symptoms at three months after stroke and functional outcome after 15 months' follow-up. We hypothesized that depression would negatively affect outcome in stroke patients (Study V).

SUBJECTS AND METHODS

Subjects

The present study is part of the Stroke Aging Memory Study (SAM), of which the detailed procedures have been described (Pohjasvaara et al., 1997). Briefly, all 1622 patients admitted to Helsinki University Central Hospital with symptoms of possible ischemic stroke were evaluated for inclusion by a clinical neurologist. Stroke was diagnosed in 1447. Further inclusion criteria were:

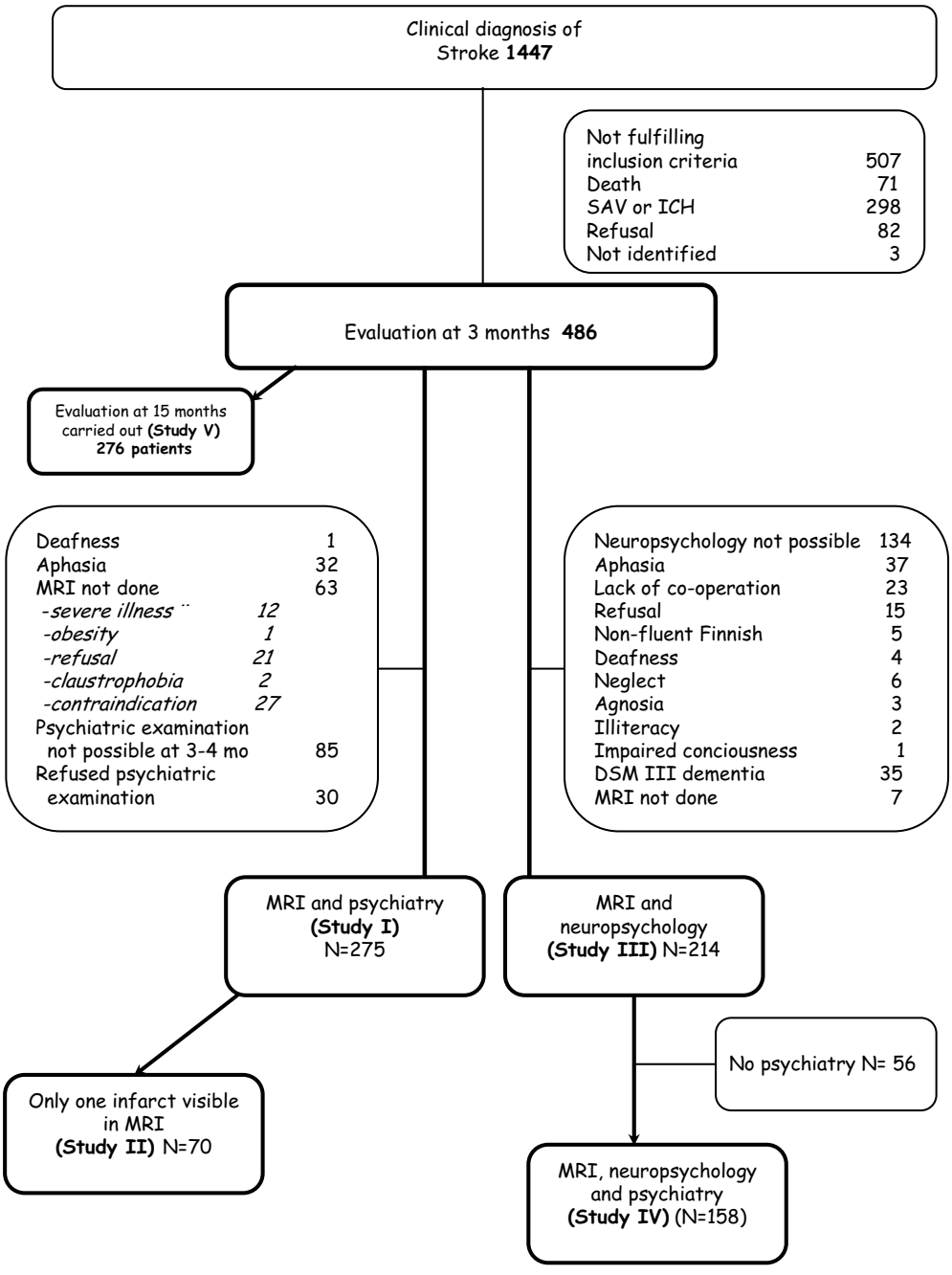
- Age 55 to 85 years
- Fulfilling the current criteria for stroke (WHO, 1989, NINDS, 1990, NASCET, 1991).
- Symptoms not caused by subarachnoidal or intracerebral hemorrhage
- Residence in the city of Helsinki
- Mastery of the Finnish language

All 642 patients fulfilling the inclusion criteria were invited to a follow-up visit to be held three months after stroke. Of those invited, 71 (11.1%) had died before this visit, 82 (12.8%) refused, and 3 (0.5%) could not be reached. A total of 486 patients were thus included in the SAM cohort.

No difference existed between the ages of the 85 who refused or could not be reached, and of those included (79.2±7.7 vs. 71.2±7.6 years, NS). However, those patients not included were more often female (67.1% vs. 49.2%, $P<0.05$) and were more often living in institutions at the time of examination (60.0% vs. 16.8%, $P<0.001$).

Three months after the index stroke, board-certified neurologists carried out a detailed structured clinical and neurological examination. A senior neurologist reviewed all the cases. According to the study protocol, a psychiatrist and a neuropsychologist then examined the patients, followed by MRI of the head as well as basic laboratory evaluations. The cohort of patients recruited for psychiatric examination was smaller (N=275) than the basic study cohort (N=486). This resulted from a shorter recruitment period for patients for psychiatric evaluation: the recruitment of consecutive patients for the psychiatric study started three months after, and ended one month before the recruitment period for other procedures.

Figure 1. Patient flow



At 15 months after the index stroke, the patients were contacted to arrange a follow-up visit to a neurologist or study nurse, or if not possible, a telephone interview with the patient and a knowledgeable informant (usually a caregiver).

A different cohort of the original 486 patients took part in each of the separate studies (I to V) of the present work because of different exclusion criteria and reasons for dropout in individual studies. The patient flow and reasons for non-enrollment are presented in Figure 1. The most common reason for exclusion in Studies I, II, and IV was lack of a psychiatric examination. Enrollment of patients for this examination started somewhat later than for other assessments, thus diminishing the cohort size. Patients excluded from psychiatric evaluation (Studies I, II, IV, and V) were more often dependent in ADL (52% vs. 35%, $P<0.001$), had more severe physical handicaps [Barthel Index (BI) score 16.5 vs. 18.4, $P<0.001$] , more cognitive disturbances as measured by MMSE (24.5 vs. 25.8 pts, $P<0.05$) and a more severe stroke as measured by the Scandinavian Stroke Scale (SSS) (50.2 vs. 54.0, $P<0.001$).

The Study I included 275 patients who had MRI and a psychiatric examination. Patients with a history of depressive disorders (N=54, 19.6%) and previous stroke (N=83, 30.2%) prior to the index stroke were included. Reasons for exclusion are indicated in Figure 1.

For Study II, we excluded patients with no visible brain infarct (N=13) or more than one infarct (N=192); patients with other previous psychosocial stress factors except stroke, and patients with previous depressive episodes were also excluded. The remaining 70 patients were considered to represent purely stroke-related depression. The excluded patients did not differ from those included (N=70) with regard to sex, age, or functional status in ADLs as assessed by the BI (data not shown). Neither the cognitive differences as defined by MMSE score (excluded vs. included, 25.7±4.0 vs. 26.0±4.0, P=NS, Mann-Whitney test) nor percentage of patients with DSM III R diagnosis of dementia (excluded vs. included, 19.6% vs. 15.4%, P=NS, χ^2 -test) reached statistical significance between the two groups.

For Study III 90 patients were excluded from the original 486. Reasons for exclusion were severe aphasia (n=37), lack of cooperation (n=23), refusal (n=15), non-fluency in Finnish (n=5), severe hearing or visual impairment (n=4), severe neglect (n=3), illiteracy (n=2), or reduced level of consciousness (n=1). The remaining 396 patients were eligible for neuropsychological testing and MRI. Extensive neuropsychological testing focusing on executive functions proved to be too demanding for 134 patients. These patients belonged to the more elderly and the cognitively more impaired group, in whom fatigue often prevented completion of the test protocol. An additional six patients were excluded

because of cognitive deficits (neglect, n=3; visual agnosia, n=2; and neglect with visual agnosia, n=1), and seven patients had not undergone MRI. Patients with dementia (N=35) according to the DSM III criteria were excluded. Thus, the final number of patients in Study III was 214. We compared the excluded (N=272) and included (N=214) patients and found the excluded patients to be older (72.8±7.7 vs. 69.1±7.1 years, P<0.001), more often dependent (62.5% vs. 16.4%, P<0.001), had had a more severe stroke as measured by SSS (4.9±6.4 vs. 1.4±2.6 points, P<0.001), were more impaired in activities of daily living as measured by the BI (16.1±5.3 vs. 19.5±1.7 points, P<0.001) and had more cognitive deterioration as measured by the MMSE (22.9±5.4 vs. 27.6±2.0 points, P<0.001).

Study IV included all patients from the Study III cohort who had also undergone psychiatric evaluation.

For Study V, we enrolled those 276 patients whom we were able to evaluate at 15 months after stroke. Of the original 486, 25 had died, 5 could not be reached, and 66 could not be assessed in detail. In the remaining 390 patients, BDI could be completed in 276 patients 15 months after stroke. When we compared the 210 excluded patients with the 276 included, no difference existed in sex, stroke lesion localization, or history of previous stroke. The patients not included were, however, significantly older (73.1±7.4 vs. 69.8±7.5; P<0.001), more depressed as measured by the BDI at three months (10.9±8.1 vs. 8.9±6.7; P<0.01), more dependent in ADL functions as measured by the Barthel Index (BI, 19.0±2.5 vs. 15.7±5.7, P<0.001), more handicapped as measured by the Rankin Scale (2.8±1.3 vs. 1.9±1.0; P<0.001), and had a lower grade of education than those included (38.7% vs. 26.6%; P<0.01).

For neuropsychological definition of executive dysfunction, the control group was 28 healthy elderly subjects (mean age 67 years, range, 61 to 76) recruited from a community-based larger sample.

Methods

1. Clinical neurological examination

Neurological examinations were performed by two board-certified neurologists. The Mini-Mental State Examination (MMSE, maximum, 30; Folstein, 1975) was used to assess global cognitive functioning.

The ability to carry out basic and instrumental activities of daily living and stroke-related impairment and handicap, as well as stroke severity, were assessed by structured interview of both the patient and a knowledgeable informant, and by a neurologist's evaluation. The following scales assessed the basic and instrumental activity of daily living, stroke-related impairment and handicap, and stroke severity:

- Instrumental Activities of Daily Living (IADL; maximum, 8, for instrumental activities of daily living) (Lawton and Brody, 1969)
- Functional Activities Questionnaire (FAQ, for activities of daily living, maximum, 30) (Pfeffer et al., 1982)
- Barthel Index (BI, maximum 100, for handicap) (Mahoney F.I., 1965)
- Rankin Scale (RS; maximum 5, for impairment) (Rankin, 1957)
- The 21 /item Beck Depression scale (BDI; Beck and Beck, 1972)
- Scandinavian Stroke Scale (SSS; maximum 58, for stroke severity) (Scandinavian Stroke Study Group, 1985)

Dependency was defined as described by Tatemichi et al. (1994). The patient was classified as being dependent if he required daily assistance or home attendant help or was living in a nursing home or other institution.

2. Psychiatric examination

The majority of patients (n=220) were examined by a senior psychiatrist, who also supervised the data entry of patients (n=55) examined by a resident psychiatrist. Both were blinded to the radiological data. The clinical psychiatric examination was carried out after the MRI examination at 12 to 20 weeks (mean ± SD; 15.5±1.7) after the index stroke. The examination included a computer-assisted structured interview, Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990). The main content of the SCAN is the 10th version of the Present State Examination (PSE-10 Wing, 1974). The earlier version (PSE 9) has been widely used in research concerning the elderly and the physically ill patients. The Gatego-5 program computed a measure of the severity of any psychopathology present, and the program suggested a profile for the DSM-III-R (APA, 1987) categories. The severity and quality of depres-

sive symptoms were assessed by the Montgomery and Åsberg depression rating scale (MADRS) (Montgomery and Åsberg, 1979), and those of anxiety by Zung Anxiety Score (SAS) (Zung, 1971). The Global Assessment of Functioning Scale (GAF) was used to rate overall psychological, social, and occupational functioning. The information concerning possible previous depressive episodes was obtained by interviews with the patients, relatives and caregivers. For the final diagnoses of depressive disorders, data from the clinical psychiatric examination, interviews, psychiatric rating scales, and the SCAN protocol were combined.

Patients with depression post-stroke included those subjects with DSM-III-R major depressive disorder (single or recurrent episode), bipolar disorders (depressed episode), organic mood disorder (organic depressive disorder), adjustment disorder (depressed or mixed anxiety and depressed mood), dysthymic disorder, dementia with depressed mood (as defined in the DSM-IV), and major depressive disorder in partial remission.

3. Neuropsychological examination

The neuropsychological examination included a set of tests covering different aspects of executive function. The number of perseverative errors and number of categories on Nelson's version of the Wisconsin Card Sorting Test (Nelson, 1976) was used to assess perseveration, flexibility, and ability to shift set (Arnett et al., 1994, Glosser and Goodglass, 1990, Perrine, 1993). A shorter version of the Stroop test (Perret, 1974) measured susceptibility to interference, flexibility, and capacity to inhibit over-learned responses (MacLeod, 1991, Lowe and Rabbitt, 1997, West and Bell, 1997). In a similar manner, two variables from the Trail-Making A- and B- tests were used to assess maintaining and shifting sets (Burgess et al., 1998, Arbuthnott and Frank, 2000, Wecker et al., 2000, Reitan, 1958). Verbal fluency evaluated by semantic category (animal naming in one minute) and letter generation (words beginning with the letter "k" in one minute) (Lezak, 1995) served as a measure of effective memory search strategy (Crowe, 1992).

Executive dysfunction has no generally accepted and uniform definition. We used the performance of the control group to calculate standardized score for eight variables: Wisconsin number of categories, number of perseverative errors, Stroop division score of set B and interference score, Trail Making score of set B and ratio between sets A and B, and the two verbal fluency scores. The sum score from the eight variables was compared with that of the control subjects. Those patients whose performance fell below 1.5 SD of the control group's mean score were defined as having executive dysfunction.

4. Follow-up visit at 15 months

The assessment included the MMSE, the BI, and the BDI. Information for the scales came from the patient, or in some cases from the relatives or caregivers, if the patient was unable to comply. The information was gathered by a neurologist or by a trained study nurse.

Those patients with a RS scale grade of I or II, and BI points ≥17 were defined as having a good functional outcome, and those patients who scored worse were defined as having a poor outcome (Kotila et al., 1999). A BDI cutpoint of ≥10 points was used for depression (Pohjasvaara et al., 1998b). The sensitivities and specifities of this cutpoint when compared to the PSE/based diagnosis at three months were 0.73 and 0.67 for major depression, and 0.73 and 0.62 for minor depression.

5. MRI methods

MRI was performed with a 1.0 T system three to four months after the stroke. The images were reviewed by a neuroradiologist blinded to the clinical data. To test the reliability of the visual rating, the same rater reviewed 60 MRI scans independently, and the results were compared to those of another neuroradiologist and a general radiologist. For the reliability of rating WMCs, the weighted kappa values for intraobserver agreement were 0.72 to 0.95 and for interobserver reliability 0.72 to 0.93. For the reliability of rating brain atrophy, the intraobserver reliability was 0.75 to 0.82, and the interobserver reliability was 0.61 to 0.74.

The number, type, side, site, and size of lesions were recorded. Lesions equivalent to the signal characteristics of cerebrospinal fluid on T1-weighted images and measuring over 3 mm in diameter, as well as wedge-shaped cortico-subcortical lesions, were regarded as brain infarcts. The volume of the lesion was estimated by the formula for calculating the volume of the ball. We grouped the infarcts into 4 categories based on their largest diameter (3 to 9 mm, 10 to 29 mm, 30 to 59 mm, and over 60 mm), and the radii used for calculations were 3, 10, 20, and 30 mm, respectively.

The number and volumes of infarcts affecting different anatomical sites were evaluated a) on both sides, b) on the right side, and c) on the left side separately. The sites included: a) brain lobes (cortical-subcortical lesions in frontal, temporal, parietal, and occipital lobes; b) vascular territories (deep and superficial anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), internal cerebral artery and border-zone areas) and c) specific locations: medulla, pons, cerebellum, optic radiation, thalamus, caudate, puta-

men, pallidum, genu of internal capsule, anterior and posterior capsule, anterior and posterior corona radiata, anterior and posterior centrum semiovale, genu, body and splenium of corpus callosum, angular gyrus, hypothalamus, hippocampus, and amygdala. Prefrontal-subcortical circuits (Cummings, 1993) include afferent basal ganglia connections from the frontal cortex to the caudate, pallidum, and thalamus; and efferent thalamocortical connections via genu of the internal capsule, anterior capsule, anterior corona radiata, and anterior centrum semiovale back to frontal cortex.

WMCs were rated on proton density-weighted images in six areas: around the frontal and posterior horns and along the bodies of the lateral ventricles, in subcortical, deep, and watershed areas (Mäntyla et al., 1997,1999). Periventricular WMCs around the frontal and posterior horns were classified based on size and shape into small cap (≤5 mm), large cap (6–10 mm) or extending cap (>10 mm); and WMCs along the bodies of lateral ventricles into thin lining (≤5 mm), smooth halo (6–10 mm), or irregular halo (>10 mm). WMCs in the subcortical, deep, and watershed areas were classified based on size (greatest diameter) and shape into small focal (≤5 mm), large focal (6–10 mm), focal confluent (11–25 mm), diffusely confluent (>25 mm), and extensive WMC (diffuse hyperintensity without distinct focal lesions affecting the majority of the white matter area). The number for each type of hyperintensity was counted, and extensive WMCs were rated as absent or present. Moderate and severe degree of WMCs included large and extending caps in the periventricular area; smooth halo and irregular halo along the bodies of lateral ventricles; and focal confluent, diffusely confluent, and extensive WMCs in the subcortical, deep and watershed areas. The extent of WMCs was also graded on the four-point scale of Fazekas et al (1987).

Brain atrophy was rated as none, mild, moderate, or severe, by comparison with standard images according to the methods of Scheltens et al (1992) and Erkinjuntti et al (1993). Cortical atrophy was rated in frontal, parietal, and occipital lobes, central atrophy in temporal, frontal, and occipital horns and bodies of the lateral ventricles, and medial temporal lobe atrophy in the entorhinal cortex and hippocampus. Cortical and central atrophy was expressed as the mean of the rating in all the bilateral areas rated and divided into two groups: none to mild vs. moderate to severe atrophy.

Data analysis and statistics

The Fisher exact test (2-tailed) was applied for categorical data and the Mann-Whitney non-parametric test for continuous data in Studies I to IV. In Study V, the χ^2 -test was applied for categorical data, and the pooled t-test for continu-

ous data. No adjustments were made for multiple comparisons in statistical approaches. The α-level of significance was $P < 0.05$ throughout. Logistic regression models were used for the analyses of significant contributors of PSD, executive dysfunction, and DES. The statistics were analyzed with the BMDP (1994) and SAS (1990) programs.

Ethical approval and informed consent

The study was approved by the Ethics Committee of the Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland. The study design was first fully explained, and written information was provided to the patients; and if they agreed to participate, they signed an informed consent.

RESULTS

Prevalence of post-stroke depression and executive dysfunction

Of the 275 patients for whom both the psychiatric and MRI examination were carried out in Study I, some depressive disorder was diagnosed in 109 (39.6%). For clinical diagnoses see Table 4. Of the 109, the post-stroke depressive episode was the first ever for 77 (71%), with one or more depressive episodes before the index stroke for the 32 (29%) others.Of the 275 patients, antidepressive medication was used by 63 (22.9%) at three months' follow-up. For 57 of these 63 patients, the antidepressant was prescribed first after the index stroke, and 42 of those 63 patients belonged to the depressed group of 109 patients.

Table 4. Depressive disorders by DSM–IV categories in the Helsinki Stroke Aging Memory Study cohort. N total = 109

Major depression	**Number (%)**
Depressive disorder due to stroke	5 (1.8)
Vascular dementia with depressed mood	13 (4.7)
Major depressive disorder, single episode	42 (38.5)
Major depressive disorder, recurrent	11 (4.0)
All major depression	71 (25.8)
Minor depression	
Dysthymic disorder	1 (0.4)
Adjustment disorder with depressed mood	22 (8.0)
Adjustment disorder with anxiety and depression	9 (3.3)
Major depressive disorder, in partial remission	4 (1.4)
Depressive disorder not otherwise specified	2 (0.7)
All minor depression	38 (13.8)

Depression was not associated with age, sex, education, handedness, or cognitive function as measured by the MMSE, but the depressed patients were more impaired in activities of daily living, as indicated by the difference in the BI score; they had more severe stroke, as indicated by the SSS score; and more often they took antidepressive medications.

Executive dysfunction was found in 73 (34.1%) of the 214 patients (Study III). Patients with executive dysfunction were older, had a lower level of education, were more often dependent, and had lower MMSE scores than did those pa-

tients without executive dysfunction. There were no significant differences in male/female ratio, in ADL functions as measured by the BI, or in presence of depression (39% vs 39.6%, χ^2 test, P=NS).

Lesion location in a naturalistic patient sample (Study I)

Most patients had more than one brain infarct on MRI. Twelve patients with no lesion fulfilling the radiological criteria (lesion diameter larger than 3 mm) were, however, included in the study because they fulfilled the clinical criteria for ischemic stroke.

The total number of brain infarcts was 3.2±2.5 (mean ± SD): right hemisphere 1.7±1.6, and left hemisphere 1.6±1.4. There were no differences in overall number of brain infarcts or in those affecting either the left or right hemisphere between patients with and without PSD. The patients with PSD, however, more frequently had lesions affecting the prefrontal-subcortical circuits. Within these circuits, especially the caudate, the pallidum, the genu of the internal capsule, and the anterior capsule were more often affected (Table 5), also with a left-sided predominance for brain infarct location in these structures in the depressed patients. Occipital brain infarcts in the right hemisphere were less common in patients with PSD (Table 5).

Table 5. Mean number (SD) of brain infarcts in patients with and without depression post-stroke in Study I.

Site	Depression present N=109	Depression absent N=166	P
Occipital lobe (right side)	0.09 (0.32)	0.18 (0.41)	<0.05
Caudate (either side)	0.48 (0.69)	0.31 (0.60)	<0.05
Caudate (left side)	0.27 (0.49)	0.15 (0.41)	<0.05
Pallidum (any side)	0.54 (0.73)	0.32 (0.61)	<0.01
Pallidum (right side)	0.27 (0.45)	0.17 (0.39)	<0.05
Pallidum (left side)	0.27 (0.44)	0.15 (0.36)	<0.05
Genu of internal capsule (left side)	0.11 (0.31)	0.03 (0.17)	<0.01
Anterior capsule (left side)	0.16 (0.36)	0.06 (0.24)	<0.01
Posterior corona radiata (either side)	0.49 (0.63)	0.32 (0.50)	<0.05
Posterior corona radiata (left side)	0.26 (0.46)	0.15 (0.35)	<0.05
Amygdala (either side)	0.05 (0.21)	0.006 (0.08)	<0.05
Frontal-subcortical circuit (either side)	1.56 (1.61)	1.16 (1.39)	<0.05
Frontal-subcortical circuit (left side)	0.86 (1.0)	0.57 (0.85)	<0.05

Mann-Whitney non-parametric test. Only those areas differing between depressed and not depressed patient groups shown.

No differences occurred in total volume of the brain infarcts as a whole or in either left or right hemispheres between the PSD and non-PSD patients (See Study I, Table 4., page 929). However, the depressed patients had significantly larger lesions affecting the deep MCA territory, caudate, pallidum, genu and anterior part of the internal capsule, posterior corona radiate, and the amygdala, with a left-side predominance. In contrast, patients without PSD had larger brain infarcts affecting the right occipital lobe.

Patients with major depression (N=71) had significantly more infarcts affecting the frontal-subcortical circuit structures than did patients with minor depression (1.8±1.7 vs. 1.2±1.4; df=197, P<0.05, Mann-Whitney test). No difference appeared in frequency of brain infarcts affecting any of the substructures (e.g., pallidum, caudate) of frontal-subcortical circuitry between these two groups. No differences between the depressed and not depressed patient groups occurred in the percentage of moderate to severe degree of WMCs, in the mean Fazekas White Matter Lesion score or in the extent of central, cortical, or medial temporal atrophy.

There were no differences in the volumes of infarcts, severity of WMCs, or extent of atrophy between patients with first-ever (n=77) or recurrent depressive episode (n=32). Patients with a first-ever depression episode after the index stroke had a lower frequency of brain infarcts than did the patients with previous episodes of depression (2.8±2.4 vs. 4.1±2.6; P<0.05, df = 107; Mann-Whitney test). This effect was even clearer in the number of right-side brain infarcts (1.3±1.5 vs. 2.3±1.8, P<0.01). Patients with their first-ever depression also had significantly fewer infarcts in the superficial medial cerebral artery area (0.88±1.1 vs. 1.2±1.1, P<0.05).

Antidepressive medication was used by 63 (22.9%) of the 275 patients at 3 months' follow-up. For 57 of these patients, the antidepressant was prescribed first after the index stroke, and 42 of these patients belonged to the depressed group of 109 patients.

Logistic regression analysis showed that the significant contributors for PSD were mean frequency of infarcts in the left genu of the internal capsule (N=275; OR 3.2; 95% CI 1.0–10.1), mean frequency of infarcts in the pallidum of either side (OR 1.6; 95% CI 1.1–2.3), and mean volume of infarcts in the right occipital lobe (OR 0.98; 95% CI 0.96–0.99).

Lesion location in patients with only one infarct (Study II)

Stroke-related depression was present in 26 (37.1%) of the 70 patients with one single brain infarct. Table 6 shows the distribution of patients according to location of infarct. In this subanalysis we counted the number of patients with brain infarcts affecting specific brain areas. Patients with depression more often had a brain infarct affecting the basal ganglia, mainly caudate, the putamen, and pallidum, as well as the posterior corona radiata.

Table 6. Number (%) of patients with brain infarcts at various anatomical sites with and without depression post-stroke in Study II.

Site	Number of affected patients with depression (n=26)	Number of affected patients without depression (n=44)	P
Occipital lobe (either side)	4 (15.4)	0 (0)	<0.05
Caudate (either side)	7 (27.0)	3 (6.7)	<0.05
Caudate (left side)	5 (19.2)	1 (2.3)	<0.05
Putamen (either side)	9 (34.6)	5 (11.4)	<0.05
Pallidum (either side)	9 (34.6)	3 (6.8)	<0.01
Pallidum (left side)	6 (23.1)	2 (4.5)	<0.05
Posterior corona radiata (either side)	14 (53.8)	11 (25.0)	<0.05

Fisher exact test, two-tailed. Only areas differing between depressed and not depressed patient groups shown.

The volumes of the brain infarcts that affected specific sites were larger in the patients with PSD at the following sites (cm^3, ± SD): frontal lobes (either side, 30.4±51.1 versus 7.4±2.5, P<0.05 Mann-Whitney non-parametric test), anterior corona radiata (either side, 33.0±50.3 versus 7.5±24.8, P<0.05), posterior corona radiata (either side, 34.8±49.5 versus 8.7±25.0, P<0.01; left side 17.0±36.9 versus 3.5±17.6, P<0.05), posterior centrum semiovale (either side, 30.1±47.5 versus 10.9±29.5, P<0.05), amygdala (either side 13.0±36.8 versus 0.0±0.0, P<0.05), putamen (left side, 15.8±36.9 versus 2.6±17.0, P<0.05), pallidum (left side, 15.8±36.9 versus 2.6±17.0, P<0.05), frontal-subcortical circuit (either side, 133.9±22.8 versus 33.1±13.1, P<0.05).

The extent of WMCs in the periventricular areas, centrum semiovale, subcortical areas, watershed areas, or in the mean Fazekas WMC score did not differ between the depressed and non-depressed patient groups. Further, no difference appeared between the two groups in the grade of cortical, central, or medial temporal brain atrophy (data not shown).

In the logistic regression model, the infarct localization in the pallidum of either side was the only correlate with PSD (OR 7.2; 95% CI 1.9-35.7).

MRI correlates of executive dysfunction (Study III)

The locations that were significantly more often affected by brain infarcts in patients with executive dysfunction are shown in Table 7. The more brain infarcts, the more likely the patient was to have executive dysfunction, especially when the brain infarcts were located in the left hemisphere. Lesions affecting the frontal-subcortical circuits also were associated with executive dysfunction, and even more clearly so in the left hemisphere. Of the 73 patients with executive dysfunction, 21 (28.8%) had a brain infarct affecting the pons, compared with 19 (13.5%, χ^2 test, P<0.01) of the 141 patients without executive dysfunction. Patients with pontine infarcts had a higher total number of brain infarcts than did other patients (4.1±2.7 vs. 2.8±2.3, Mann-Whitney test, P<0.01). They also had a more severe degree of white matter changes as measured by Fazekas white matter scoring (mean, 1.75±0.85 vs. 1.40±0.72, Mann-Whitney test, P<0.05).

Table 7. Mean (SD) number of brain infarcts in patients with (N=73) and without (N= 141) executive dysfunction after stroke.

Site	Executive dysfunction present	Executive dysfunction absent	P value
All sites	3.66 (2.64)	2.76 (2.30)	<0.05
Left side	1.93 (1.61)	1.26 (1.34)	<0.01
Anterior cerebral artery superficial (either side)	0.33 (0.65)	0.12 (0.47)	<0.01
Anterior cerebral artery superficial (left side)	0.20 (0.50)	0.06 (0.26)	<0.01
Middle cerebral artery superficial (either side)	1.11 (1.16)	0.79 (1.01)	<0.05
Middle cerebral artery superficial (left side)	0.61 (0.74)	0.33 (0.54)	<0.01
Pons	0.33 (0.55)	0.15 (0.40)	<0.01
Pons (left side)	0.15 (0.36)	0.04 (0.20)	<0.01
Putamen (left side)	0.33 (0.50)	0.19 (0.41)	<0.05
Pallidum	0.50 (0.67)	0.29 (0.60)	<0.05
Anterior corona radiata (left side)	0.19 (0.40)	0.08 (0.30)	<0.05
Anterior centrum semiovale (left side)	0.16 (0.37)	0.07 (0.28)	<0.05
Posterior centrum semiovale (left side)	0.30 (0.49)	0.11 (0.31)	<0.001
Frontal-subcortical circuit (either side)	2.59 (2.18)	1.74 (2.18)	<0.001
Frontal-subcortical circuit (left side)	1.37 (1.42)	0.77 (1.32)	<0.001

Mann-Whitney non-parametric test. Only areas differing between the two groups shown.

Moderate to severe white matter changes were more frequent in patients with executive dysfunction (See Study III, Table 3., page 629). Further, moderate to

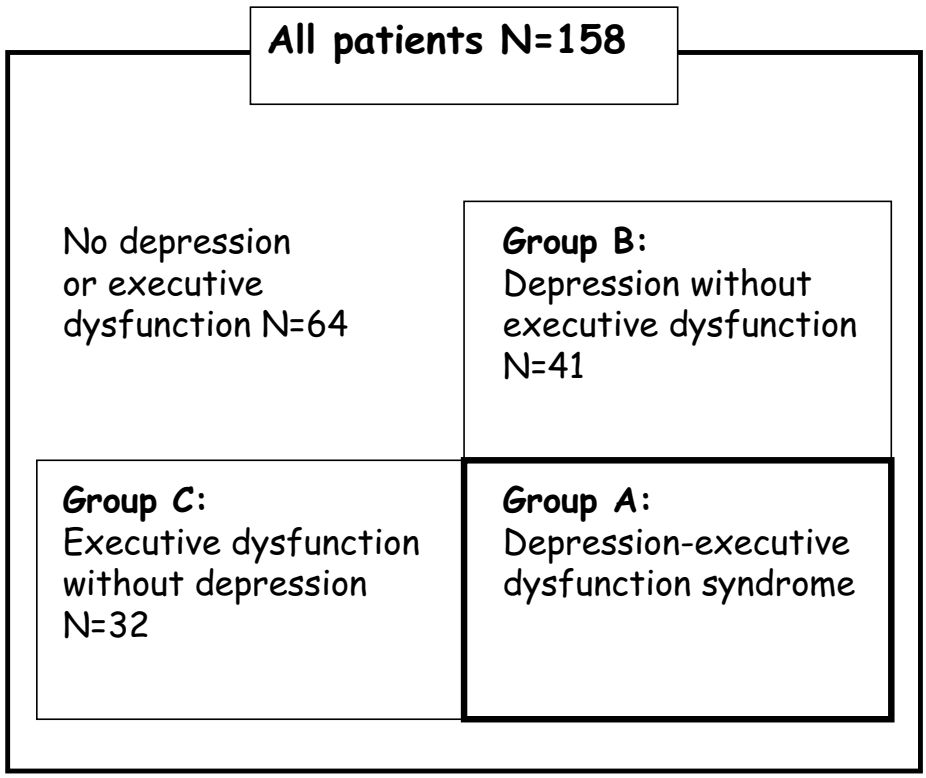
severe central and medial temporal atrophy was more frequent in patients with executive dysfunction.

In the logistic model, independent correlates of executive dysfunction were MMSE score (OR 1.6, SD 1.3–1.9), low education (OR 2.5, SD 1.1–5.6), frequency of left-sided pontine infarcts (OR 3.9, SD 1.1–14.2), frequency of infarcts in the posterior centrum semiovale (OR 4.1, SD 1.8–9.8), moderate to severe medial temporal atrophy (OR 2.3, SD 1.0–5.2), and Fazekas white matter score (OR 1.6, SD 1.0–2.6).

Depression-executive dysfunction syndrome (Study IV)

Depression was present in 62 (39.2%), executive dysfunction in 53 (33.5%), and DES in 21 (13.3%) of the 157 patients (see Fig. 2). Patients with DES had more severe cognitive dysfunction (lower score in the MMSE), more severe depression (higher score in the MADRS), lower level of psychosocial functioning (lower scores in the GAF), and their complex ADL scores were lower (Table 8) than were those of the patients without DES.

Figure 2. In statistical analysis of Study IV, patients in group A compared with all other patients, then with patients in groups B and C.



Depressive patients with executive dysfunction had a lower MMSE score than did those depressive patients without, and they were more often prescribed antidepressive medication. Within the depressive patient group there was no difference between those with, and those without executive dysfunction in sex distribution, education level, dependence, presence of previous depressive episodes, age, SSS score, Rankin score, the BI or GAF score (Table 8).

Table 8. Characteristics of patients with DES, with depression without executive dysfunction, and without DES, after stroke.

	Patients with DES* (N=21)	P	Patients with depression and without executive dysfunction ** (N=41)	P	Patients without DES (N=137)
Female sex (%)	8 (38.1)	n.s.	23 (66.1)	n.s.	68 (49.6)
Age (SD)	68 (8.2)	n.s.	68.9 (7.6)	n.s.	69 (6.6)
Low educational level (%)	6 (28.7)	n.s.	7 (17.1)	n.s.	27 (20.0)
Functional independence at 3 months (%)	16 (76.2)	n.s.	34 (82.9)	n.s.	120 (87.6)
Use of antidepressive medication (%)	15 (71.4)	<0.001	17 (41.5)	<0.05	17 (12.5)
Previous depressive episode	29 (21.2)	n.s.	14 (34.1)	n.s.	6 (28.6)
SSS (SD)	56.4 (4.4)	n.s.	55.6 (4.8)	n.s.	56.7 (3.8)
Rankin (SD)	1.8 (0.8)	n.s.	1.8 (0.9)	n.s.	1.59 (0.9)
bADL (SD)	5.6 (6.4)	n.s.	3.5 (4.1)	n.s.	2.8 (4.9)
cADL (SD)	5.9 (2.1)	<0.05	6.7 (1.5)	n.s.	7.0 (1.5)
MMSE (SD)	25.8 (2.2)	<0.001	27.8 (2.2)	<0.001	27.8 (1.8)
GAF (SD)	70.6 (7.0)	<0.01	71.3 (6.0)	n.s.	74.9 (5.8)
SAS yht (SD)	29.0 (5.4)	n.s.	32.9 (9.0)	n.s.	28.1 (7.3)
MADRS (SD)	22.0 (11.8)	<0.01	18.6 (9.7)	n.s.	8.1 (9.1)

Fisher's exact test (2-tailed) was used for categorical data and the Mann-Whitney non-parametric test for continuous data. * = compared between patients with and without DES, ** = compared between patients with depression, with and without executive dysfunction. SSS = Scandinavian Stroke Scale; bADL = basic activities of daily living; cADL=complex activities of daily living; MMSE = Mini Mental State Examination; GAF = Global assessment of psychological, social and occupational functioning; SAS = Self-report anxiety inventory; MADRS = Montgomery-Åsberg depression rating scale.

Scores of scales measuring severity of anxiety (SAS) or depression (MADRS) did not differ between patients with DES and those with depression without executive dysfunction, although both scores tended to be higher in patients with DES.

The anatomical sites significantly more often affected in patients with DES are presented in Table 9. In patients with DES, the mean number of brain infarcts was higher in many structures contributing to the frontal-subcortical circuit, when compared to patients without DES. Further, when depressive patients with executive dysfunction were compared with depressive patients without executive symptoms, the patients with DES had more lesions in a similar fashion affecting these frontal-subcortical structures (Table 9).

Table 9. Frequency (SD) of brain infarcts affecting different brain locations in patients with DES, depression without executive dysfunction, and without DES after stroke.

	Patients with DES* (N=21)	**P**	**Patients with depression and without executive dysfunction** (N=41)**	**P**	**Patients without DES (N=137)**
Left side (all)	2.4 (1.7)	<0.01	1.2 (1.3)	<0.01	1.5 (1.7)
Left superior medial cerebral artery	0.76 (0.83)	<0.05	0.2 (0.5)	<0.01	0.39 (0.61)
Caudate	0.57 (0.75)	<0.05	0.5 (0.8)	n.s.	0.33 (0.64)
Left anterior capsule	0.24 (0.44)	<0.01	0.05 (0.2)	<0.05	0.05 (0.22)
Pallidum	0.71 (0.71)	<0.01	0.4 (0.7)	<0.05	0.30 (0.62)
Left pallidum	0.33 (0.48)	<0.05	0.1 (0.3)	<0.05	0.12 (0.33)
Left posterior corona radiata	0.33 (0.56)	<0.05	0.1 (0.3)	n.s.	0.12 (0.32)
Left posterior centrum semiovale	0.43 (0.51)	<0.001	0.07 (0.3)	<0.001	0.12 (0.33)
Frontal-subcortical circuits all	3.1 (2.8)	<0.05	2.0 (2.6)	<0.05	1.9 (2.2)
Frontal-subcortical circuits left	1.9 (1.5)	<0.001	0.9 (1.5)	<0.01	0.84 (1.4)

Mann-Whitney non-parametric test. * = compared between patients with and without DES. ** = compared between patients with depression with, and without executive dysfunction (groups A and B, Fig.2.) Only those areas differing between patients with and without DES shown.

Patients with and without DES did not differ in extent of or in white matter changes, or in the severity of central, cortical, or medial temporal lobe atrophy.

In the logistic models, the only correlate with DES was number of brain infarcts affecting frontal-subcortical circuits on the left side (OR 1.6; 95% CI 1.1–2.5).

Depression as a predictor of poor long-term functional outcome (Study V)

Depression as defined by the BDI cutpoint of ≥10 points was present in 43.9% of the patients at three months, and in 44.6% of the patients at 15 months post-stroke. Only 31.9% of the depressed patients took antidepressive medication at three months after stroke, but this medication did not affect the functional outcome at 15 months (RS I–II, 33.9% vs. 31.8%).

Major depression or depression as defined by a BDI cutpoint of ≥10 were associated with a poor functional outcome at 15 months, whereas this association was lacking in patients with minor depression (Table 10).

Table 10. Association of depression at three months post-stroke with functional outcome as measured by the Rankin Scale at 15 months (%).

Definition of depression	RS I–II	RS III–IV	All	P
Psychiatric examination	163	93	256	
DSM III R major depression	34 (20.9)	32 (34.4)	66 (25.8)	<0.05
Minor depression	12 (13.0)	20 (12.2)	32 (12.5)	n.s.
Evaluated by BDI	154	236	390	
BDI≥10 depression	78 (33.1)	93 (60.4)	171 (43.9)	<0.0001

Likewise, major depression at three months was associated with a worse outcome or dependence in ADL functions as defined by a BI <17 (35.5% vs. 22.7%, $\chi^2 = 4.03$, d.f.=1).

Logistic regression analyses showed that depression (BDI≥10) at three months post-stroke correlated with poor functional outcome at 15 months (OR 2.50, 95% CI 1.60–3.76), whereas poor outcome at three months was not associated with depression at 15 months.

DISCUSSION

Methodological aspects

Anterior, and especially left anterior lesion location have been previously related to depression in many reports (Robinson et al., 1983a, Åström et al., 1993, Starkstein et al., 1988, Herrmann et al., 1995) but not in all (Gainotti et al., 1997, MacHale et al., 1998, Sharpe et al., 1990). The most influential meta-analysis in this field, by Carson et al (2000a), failed to find any proven association between lesion location and post-stroke depression. This topic is one of the greatest controversies in neuropsychiatry, seriously affected by confusion on methodological issues (Singh et al., 1998). Among the most critical issues are patient identification (i.e., adequate diagnostic procedure for depression), and accurate stroke lesion identification and characterization.

Another important factor in PSD studies is the source of subjects: usually selected from either hospital- or community-based populations. A recent systematic meta-analysis revealed among studies of hospital inpatients an association mostly between left-hemisphere stroke and depression, whereas in community-based studies, depression occurred more after right-hemisphere infarcts (Bhogal et al., 2004). It is possible that such differences reflect different practices in organizing stroke management in different areas. For instance, in Sweden, 90% of all stroke patients are admitted to a hospital (Åström et al., 1993), whereas some studies have been conducted in regions where fewer than 50% of the stroke patients are admitted to a hospital (House et al., 1990). In Finland, and especially in the catchment area of the present study, virtually every patient is treated in hospital during the acute phase of a stroke. Our original patient sample is thus representative of stroke patients in general. Among studies of lesion location and PSD, our study is also by far the largest and the first one to employ MRI technology. The largest CT-based studies in this field have recruited around 150 patients (Kim and Choi-Kwon, 2000, Gainotti et al., 1999).

It has been proposed that major and minor depression after stroke are two different disorders (Gainotti et al., 1997, Morris et al., 1994), (Paradiso and Robinson, 1999). This subject is still controversial, however, as diagnosing major vs. minor depression in post-stroke elderly patients by present diagnostic criteria is difficult (Gainotti et al., 1997). These patients often have dementia, dysphasia, or cognitive symptoms that may mimic or obscure depressive symptoms. Another important behavioral syndrome post-stroke, with key features of emotional blunting and loss of interest and motivation, is apathy, which is present

in 20% of stroke patients; and about half of these patients are also depressed (Starkstein et al., 1993). Another frequent feature of PSD is post-stroke fatigue. “Primary” fatigue – that presenting without depression – is also common, often associated with brain-stem and thalamic lesions (Staub and Bogousslavsky, 2001).

Due to these uncertainties, we did not choose to distinguish between different depressive syndromes, but included patients with any depressive disorder. It is, however, obvious that the concept of post-stroke depression needs to be re-framed. More accurate diagnostic criteria for PSD would be useful for both clinical and scientific work, and these criteria would probably in many ways be identical or analogous to the suggested criteria for vascular depression.

At 15 months’ follow-up, we chose to use BDI for identifying patients with depression. While not as accurate as a clinical psychiatric examination, it has been widely used in stroke patients (House et al., 1989a). The cut-off point of ≥10 points for depression has been useful for patients with somatic illnesses (Beck and Beamesderfer, 1974, Beck, 1988).

As executive dysfunction is a poorly defined concept, many differing methods have served to measure it (Royall et al., 2002). Even the leading authors in this field have often used narrow and one-sided instruments to evaluate this complex disorder (Alexopoulos et al., 2002), which reflects the lack of generally accepted and validated methodology. We wanted to cover the most important aspects of executive functions by using many widely used neuropsychological tests and combining their results in a sum variable. We also excluded patients with dementia, as correlations between radiological findings and many aspects of poor cognitive function in demented patients would be difficult.

Most previous CT-based studies have used simple descriptions of lesion locations such as distance from the frontal pole of the brain, and only recently have more detailed atlas-based lesion analyses been applied (Singh et al., 1998). Magnetic resonance imaging is superior to CT in detecting the site, type, and extent of infarcts, especially in the deep gray matter structures.. Sensitivity of the MRI in detecting small deep lesions is one probable factor explaining some of the differences between previous findings and ours.

Our studies have some important limitations. First, because the older, more handicapped, and more cognitively impaired patients were more often excluded from demanding neuropsychological, neuroradiological, and psychiatric examinations, our results should be generalized in elderly stroke populations with caution. Second, although MRI is more accurate than CT in localizing brain lesions, the visually analyzed scans still give only an estimate of lesion sizes

and locations. Large brain infarcts affecting, for example, the basal ganglia overlap many anatomical sites, complicating the analysis. On the other hand, small and possibly critical sites like many of the small limbic structures may remain undetected as correlates of PSD, either because stroke rarely affects them, or because they were not detailed in the radiological ratings.

MRI correlates of post-stroke depression

We first evaluated depression in the naturalistic cohort including all patients, as most of the patients treated for symptoms of acute brain infarct have, in MRI, more than one infarct visible. Indeed, our patients had on an average 3.2 brain infarcts. Any depression (minor or major) was present in 109 (40%) of the patients three months post-stroke. This is in accordance with most other findings (Table 3).

These results suggest that stroke lesion location is one of the significant factors affecting emotional and cognitive outcome in patients with stroke. Depression was related to ischemic lesions affecting the frontal-subcortical circuit, namely the caudate, the pallidum, the genu of the internal capsule, and the anterior capsule, especially in the left hemisphere. In multivariate analysis, the independent correlates of PSD were number of infarcts in the genu of the internal capsule on the left side (OR 3.2) and the number of lesions in the pallidum of either side (OR 1.6). The role of the pallidum was confirmed in the analyses in which we included only patients with one single infarct on MRI. In this model, the number of patients was reduced to only 70, but even in this model a brain infarct affecting the pallidum was a strong correlate of post-stroke depression in multivariate analysis (OR 7.2).

Evidence for the importance of the pallidum in mood regulation is emerging from neuropathological studies (Baumann et al., 1999), as well as from experience with psychiatric complications of neurosurgical treatment of Parkinson's disease (Burn and Troster, 2004). Lesions affecting the pallidum have been related to reduced glutamatergic input to the dorsolateral prefrontal cortex and to depression (Lauterbach, 1999). In both of the models, univariate analysis also revealed, however, many other locations that, when damaged by brain infarcts, were associated with depression (Tables 5 and 6). Many of these structures, e.g., the pallidum, internal capsule, and caudate, belong to the frontal-subcortical circuitry that has recently been associated with the frontal control of motor, cognitive, and emotional functions (Cummings, 1995). Laterality seems also to be important, with a left side lesion predominance in depressed patients.

Our study showed also that the volumes of the brain infarcts affecting the anatomical regions most often damaged by the infarcts in depressed patients were larger. Thus, the infarcts of the depressed patients probably were more of the large, cortical-subcortical type, rather than small lacunes. However, since large infarcts cause prominent symptoms like hemiparesis that lead patients to seek treatment promptly, the role of lacunes cannot reliably be assessed in the present material.

Other critical lesion sites in these two models were the posterior corona radiata and occipital lobes. In the first model, where every brain infarct was calculated, the right occipital location was less common in patients with depression. On the other hand, in the more restrictive model with only those patients having one and only one brain infarct, the *left* occipital lesions were associated with a higher risk for depression. This same phenomenon was reflected in the increased frequency of brain infarcts affecting the left posterior corona radiata (white matter connections from the brain stem and basal ganglia to the posterior cortex) in patients with depression. The role of the occipital lobe in depression is yet unclear, although occipital metabolic (Sanacora et al., 2004) and structural white matter changes (Kumar et al., 2004) have been reported in patients with endogenous and late-life depression.

The distinct frontal-subcortical circuits, i.e., orbitofrontal, dorsolateral, and anterior cingulate circuits, run closely adjacent to each other in the white matter connections of the internal capsule and are likely to be damaged together in case of an infarct in that area. Tatemichi et al. (1992) showed that an infarct affecting the genu of the internal capsule was related to dementia and ”frontal lobe symptoms.” It was surprising that the extent of white matter changes in different areas did not correlate with PSD, as frontal white matter lesions are one of the core features of vascular depression in general (Krishnan et al., 1997, Greenwald et al., 1998, Thomas et al., 2003b). White matter changes in PSD have not been previously studied. It is possible that the effect of white matter changes on depression is less clear in post-stroke patients than in the general elderly population, in which this association has been reported.

MRI correlates of executive dysfunction

The association between brain infarct localization and executive dysfunction has not been studied systematically before. The prevalence of executive dysfunction in our sample was 34.1, but the excluded patients were significantly older and cognitively more impaired. In such patients, executive dysfunction is common, so our prevalence of executive dysfunction is probably lower than in elderly stroke patients in general.

In case reports, lesion location in the caudate (Caplan et al., 1990), in the thalamus (Ghika-Schmid and Bogousslavsky, 2000), or in the multiple subcortical lacunae (Wolfe et al., 1990) has been associated with executive dysfunction. In our study, patients with executive dysfunction had more brain infarcts, particularly in the left hemisphere. Further, these infarcts more often affected basal ganglia (putamen and pallidum), the white matter connections therefrom (anterior corona radiata and centrum semiovale), and frontal-subcortical circuits as a whole, with left-side predominance. These findings fit well with the hypothesis that dorsolateral frontosubcortical circuits regulate executive functions (Cummings, 1995). White matter lesions have been associated with executive dysfunction (Desmond, 2002), possibly due to a disconnection between deep brain structures and cortical areas. Our results confirm the role of white matter lesions.

Periventricular, subcortical, and deep (centrum semiovale) white matter changes were clearly more extensive in patients with executive dysfunction than in those without. Analogous findings of the effects of the severity of white matter changes on executive function in patients with lacunar infarcts have also recently appeared (Wen et al., 2004). On the other hand, white matter changes may affect cognitive function in stroke patients even at early stages, when the subtle white matter changes are detected only by the more sophisticated diffusion tensor MRI technology (O'Sullivan et al., 2004).

We also found that certain posterior structures, i.e., the pons and posterior centrum semiovale, were associated with executive dysfunction. In fact, in multiple logistic regression analysis, the only anatomical brain infarct correlates of executive dysfunction were location in the left pons (OR, 3.9) and posterior centrum semiovale (OR 4.1). This may, at least in part, be explained by the fact that patients with pontine brain infarcts had a higher number of brain infarcts overall than did other patients; and that they also had more severe white matter changes than did those with other lesion locations. Thus, patients with pontine brain infarcts in our series had a more severe cerebrovascular disease, which was associated with more severe cognitive changes.

However, thalamocerebellar connections, which are further connected to frontal-subcortical circuitry, also pass through the pons. The cognitive and behavioral consequences of subtentorial stroke have received little attention (Malm et al., 1998). Our results support in part the accumulating evidence from both animal models (Keating and Winn, 2002, Winn, 1998) and patient series (Schmahmann and Sherman, 1998), of the role of thalamocerebellar circuits as a continuum with the frontal-subcortical circuits serving executive functions.

Executive dysfunction was also associated with central and medial temporal atrophy. The strong association of medial temporal atrophy with executive dys-

function may reflect emerging Alzheimer-type pathology in these non-demented patients with a heavy vascular risk-factor load. White matter changes, brain atrophy, and brain infarcts probably interact in a deleterious manner, and may lead to dementia (Pohjasvaara et al., 2000). Our findings suggest that in non-demented stroke patients the number and localization of the brain infarcts together with white matter changes and brain atrophy contribute to executive dysfunction.

Depression-executive dysfunction syndrome after stroke

In clinical practice, one often sees elderly patients recovering from stroke who also suffer from depression and whose rehabilitation seems to take longer than expected even when their depression is adequately treated. These patients often suffer from post-stroke dementia, a common complication of stroke, affecting up to one-third of elderly stroke patients (Pohjasvaara et al., 1998a). However, those patients who are not demented may suffer from a disorder that Alexopoulos has called depression-executive dysfunction syndrome (Alexopoulos et al., 2002). Although this hypothesis has attracted much interest in leading psychiatric journals, most of the papers have been produced by a single study group at Cornell University. The concept originally served to define any patient with late-onset depression – with or without stroke – in whom the depression may be caused by any age-related or vascular damage to the fronto-subcortical circuitry.

Many of our patients in our original cohort had to be excluded, and the remaining 158 patients represented the younger and the less handicapped subgroup of elderly stroke patients. Of these individuals, 21 (13.3%) had both depression and executive dysfunction. In clinical practice, where patients cannot be excluded, the proportion of DES among stroke victims is probably clearly higher. We found no differences in severity of depressive symptoms (as measured by the MADRS) between these two patient groups. However, clinicians have recognized depression in patients with DES more often than in patients without executive dysfunction: 71% of our patients with DES received antidepressive medication compared with 41% of our patients with depression without executive dysfunction.

Patients with DES had more brain infarcts affecting substructures of the frontal-subcortical circuits, especially the pallidum, anterior internal capsule, and caudate, than did our patients with DES. Within the depressed patient population, those with DES had more brain infarcts affecting mostly left-sided frontal-subcortical structures than did those depressed patients without executive dysfunction. Further, those with executive dysfunction but without depression also

had more brain infarcts affecting the length of the frontal-subcortical circuits. These results support the still somewhat hypothetical idea of anatomical circuit substrates in differing neuropsychiatric disorders. Executive dysfunction has been associated with the dorsolateral prefrontal system, and depression with the dorsolateral and orbitofrontal systems (Tekin and Cummings, 2002). Thus, stroke patients presenting with both executive dysfunction and mood disturbances should more likely have structural lesions affecting frontal-subcortical circuitry than would patients with depression but without executive dysfunction – as indeed was the case in our patients.

Our findings also suggest that the novel hypothesis of DES may be valid in stroke patients. In this subgroup of vascular depression, however, the frontal-subcortical disruption is caused by brain infarcts rather than by white-matter changes. That we found no correlation between extent of white-matter changes and DES is not surprising, since each of our patients had a severe cerebrovascular disease by definition, and the effect of brain infarcts on cognitive and mood disorders per se is probably much more robust than that of white-matter changes.

Post-stroke depression and functional outcome after stroke

The association between post-stroke depressive symptoms and consequent functional outcome has been reported in longitudinal studies (Singh et al., 2000, Kotila et al., 1999, Herrmann et al., 1998). In another of our studies from the Stroke Aging Memory cohort, we have also reported that higher BDI score at three months is associated with less independent functioning at 15 months after stroke (Pohjasvaara et al., 2002b). Each point of worsening in BDI had an independent effect on dependent living at 15 months after stroke. The present study found that those patients with depression at three months after stroke (minor or major), or patients with major, but not minor depression, had worse functional outcome, being both more handicapped (RS>II) and more dependent in activities of daily living (BI>17 points) than were those without depression after 15 months' follow-up.

Recognition and adequate treatment of depression should therefore be an important part of stroke treatment. Our patients had received a standard medical and neurological evaluation and treatment before their enrollment at three months. Of our patients with depression, 23% received antidepressive medication at three months. In community-based studies, the reported use of antidepressants in patients with PSD is less that 20% (Kotila et al., 1998). A more pragmatic and active approach in management of PSD is clearly needed, as a better outcome in rehabilitation (Narushima and Robinson, 2003) and even in survival (Jorge et al., 2003) has been associated with early antidepressive medication.

Frontal-subcortical ischemic lesions in vascular depression (Alexopoulos et al., 1997b), dysfunction of frontal-subcortical circuitry in major depression (Dunkin et al., 2000), and executive dysfunction in PSD (Downhill and Robinson, 1994) have been connected with chronicity of depression. One of the fundamental questions to be answered in future studies is the possible association of PSD with incident vascular dementia. The anatomical, subcortical correlates of PSD reported in this study are similar to those of post-stroke dementia, reported by Pohjasvaara et al (2000) from this same patient cohort, and reports of others (Tatemichi et al., 1992, Censori et al., 1996).

Vascular dementia may be caused by multiple strokes but also by a single strategic stroke, multiple lacunae, and hypoperfusive lesions such as border zone infarcts and ischemic periventricular leukoencephalopathy (Binswanger's disease) (Erkinjuntti et al., 2000b). This lesion profile is very similar or identical to that of patients with vascular depression, PSD, or DES. Thus, vascular depression and PSD should probably be considered as warning signs for emerging vascular dementia (Steffens et al., 2003), especially when cognitive disorder is already present, as in patients with DES. Recognition of PSD and prompt management of vascular risk factors may diminish that risk. Further, patients with PSD or DES may also become a target group for trials with novel compounds like galantamine (Erkinjuntti et al., 2002) or D_3 -agonists (Alexopoulos, 2001) or more specific antidepressants both to treat and to prevent cognitive decline after stroke.

CONCLUSIONS

1) Lesion location was an important determinant of PSD. Brain infarcts affecting frontal-subcortical circuitry, especially in the left hemisphere, increased the risk for PSD. The importance of subcortical lesions affecting basal ganglia and the frontal-subcortical white matter connections for PSD is highlighted.

2) Like depression, executive dysfunction was also associated with damage to the frontal-subcortical circuit structures. However, posterior lesions like pontine brain infarcts were also correlated with executive dysfunction. Further, white matter lesions and brain atrophy were important correlates of executive dysfunction post-stroke, but not PSD. Our results support the novel model of the frontal-subcortical circuit system as a regulator and modulator of cognitive functions and emotions.

3) Patients with DES had more brain infarcts affecting their frontal-subcortical structures than did those patients, who had either depression or executive dysfunction alone, or had neither. DES affected at least 13% of our elderly patients post-stroke. These patients were more disabled in activities of daily living and had more cognitive symptoms as measured by the MMSE. Further studies are needed to further characterize the phenomenology, prevalence, prognosis, and possibly more specific management options of DES.

4) Depression was an independent predictor of poor functional long-term outcome in stroke patients. We emphasize the importance of early recognition and management of depression post-stroke.

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