Depression and Cerebrovascular Disease

A phenomenological study

Paul Naarding

"We moeten niet proberen de hele symfonie in een keer te begrijpen. Laten we beginnen met de eerste drie noten…"

Vrij naar Vladimir Ashkenazy.

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Depression and Cerebrovascular Disease

A phenomenological study

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CONTENTS

Chapter 1

Cerebrovascular disease and depression An introduction

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1.1 DEPRESSION IN THE ELDERLY

Depressive disorders are among the largest groups of disorders contributing to the burden of disease in our western society, only outnumbered by cardiovascular disease. About one out of five persons will suffer from some form of depressive disorder. In general, people are often familiar with the symptoms of depression, and the subject has received increasing attention in lay conversation and literature during the past decades. However, for scientific purposes, it is hard to give a clear definition of depression and the concept has been subject to changes in definition. The current diagnosis and classification of psychiatric disorders is based on the 4th edition of the Diagnostic and Statistical Manual (DSM-IV) (see tables 1 and 2) of the American Psychiatric Association (APA) or the criteria of the 10th edition of the International Classification of diseases (ICD) of the World Health Organization (WHO) (APA 1994; WHO 1992).

The main symptoms of this syndrome are persistent sadness and anhedonia. Furthermore, there may be a range of cognitive and physical symptoms.

There are numerous factors that hamper the recognition and diagnosis of depression by GP's in the elderly compared with younger populations (van Marwijk et al. 1996).

The most important of these are the fact that most of the symptoms are not specific for depression and the absence of an external criterion for the diagnosis. Another explanation for the low number of cases detected by GP's is attribution bias. Elderly patients themselves are likely to mention their co-morbid physical health problems first, considering it inappropriate to discuss emotional problems with their GP. The complementary

Table 1: DSM-IV criteria for Mood Disorder Due to …[Indicate the General Medical Condition] (293.83)

A. A prominent and persistent disturbance in mood predominates in the clinical picture and is characterized by either (or both) of the following:
1. depressed mood or markedly diminished interest or pleasure in all, or almost all , activities
2. elevated, expansive or irritable mood

B. There is evidence from the history, physical examination or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition.

C. The disturbance is not better accounted for by another mental disorder [e.g. Adjustment Disorder With Depressed Mood' in response to the stress of having a general medical condition].

D. The disturbance does not occur exclusively during the course of a delirium.

E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify type:
With Depressive Features: if the predominant mood is depressed, but the full criteria are not met for a Major Depressive Episode
With Major Depressive-Like Episode: if the criteria are met (except criteria D) for a Major Depressive Episode
With Manic Features: if the predominant mood is elevated, euphoric, or irritable
With Mixed Features: if the symptoms of both mania and depression are present but neither predominates

Table 2: DSM-IV criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful).
2. Markedly diminished interest or pleasure in all, almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

reaction of the GP is to focus on the physical problem or to attribute the depressive symptoms to this physical health problem (Hasin & Link 1988). Of course, a good clinical and diagnostic procedure takes time, something that GP's often lack. Apart from these major explanations for low recognition, some other potential factors are provided in table 3.

Estimates of the prevalence of depression in elderly subjects vary widely. This variance is merely the result of various definitions and study-populations. The use of a clear definition and appropriate diagnostic instruments will lead to more consistent results. Arranged according to level of caseness, major depression is relatively rare among the elderly (prevalence 1.8%), minor depression is more common (prevalence 9.8%), whereas all depressive syndromes that are supposed to be clinically relevant show an average prevalence of 13.5% (Beekman et al. 1999). The prognosis of depression in the elderly is poor (Beekman et al. 2002). Medical burden increases the risk of developing depression

Table 3: Factors hampering the recognition and diagnosis of depression in the elderly (12)

Depression related	Multitude of symptoms No symptoms specific for depression No 'golden standard'
Patient related	Comorbidity: physical illness, dementia Attribution bias
Doctor (GP) related	Time constraints Lack of expertise and experience Professional beliefs and attitudes Fear of stigmatization Ageism
Interaction related	Demanding and hostile communicative style of depressed patients, leading to withdrawal and rejection by doctors

and this concerns particularly minor depression (Beekman et al. 1997a). An increased risk is found among subjects suffering from rheumatic disease, chronic pulmonary disease, but especially among subjects suffering from some form of cardiovascular disease (Beekman et al. 1995). Strokes are associated with the greatest risk for developing clinically relevant depression (Beekman et al. 1998). Depression in patients suffering from stroke and myocardial infarction is associated with poor outcome as indicated by higher levels of mortality, higher incidence of new vascular events and higher incidence of subsequent cognitive decline (Baldwin et al. 1993; Penninx et al. 2001; Penninx et al. 1998b; Pohjasvaara 2002; van Ojen 1995). The presence of a 'vascular' aetiology of depression is probably associated with a more chronic course of the depressive disorder (Beekman et al. 1997b; Mast et al. 2004a) and might be a predictor for a poor response to antidepressant medication (Fujikawa et al. 1996). These findings are of major significance for clinicians dealing with elderly patients suffering from depression as they have considerable implications with respect to treatment and provide insight into the pathogenesis of the depressive syndrome itself.

1.2 CEREBROVASCULAR DISEASE

Cerebrovascular disease can manifest itself in different ways, but by far the best known is stroke. Approximately 80% of strokes are ischemic and 20% hemorrhagic. The main subject of this thesis will be ischemic vascular disease of the brain. Cardiovascular disease is the most important burden of illness in western society nowadays. It is not only the major cause of death, but also of disability. The highest incidence of ischemic stroke is in later life, between the ages of 60-80 years, although it is not restricted to these ages. The prevalence of stroke in the Netherlands is around 170/100.000 and the incidence stands at 30,000 patients per year (van Kooten & Koudstaal 1998).

Apart from symptomatic stroke, so-called silent brain infarcts are frequently seen on cerebral scans (MRI or CT) in the elderly and they appear to be more frequent in elderly subjects with depression and dementia (Vermeer 2002). Cerebral white matter lesions are also frequently observed and probably result from cerebral small vessel disease. Arterial hypertension and older age increase the prevalence and severity of such lesions (Vermeer et al. 2002; de Leeuw et al. 2001).

1.3 POST-STROKE DEPRESSION

The incidence rate of post-stroke depression (PSD) varies from around 8% in population based studies to around 40% in patients attending specialized in-patient facilities (Robinson et al. 1984a; Stern & Bachman 1991). Explanations for these divergent findings are similar to those regarding depression in the elderly described above. Especially in the early years of research on PSD, much emphasis was put on lesion location, beginning with the work of Robinson and co-workers who found that subjects with a lesion located in the frontal left cortex were more prone to developing PSD than others (Robinson et al. 1982; Starkstein et al. 1987). Moreover, they stated that the severity of depressive symptoms depends on the distance of the vascular lesion to the frontal pole. Since then, an overwhelming amount of work has been published on this subject, some confirming his hypothesis, others not. Carson (2000) has reviewed the evidence and shown that there are no clear differences in the risk of developing depression between right- or left-sided lesions. Probably the exact location and the interference with special circuits are of more importance for developing depression than the simple subdivision into left or right. High incidence rates of depression after stroke has led to research into the efficacy of antidepressant medication, not only as a therapeutic strategy but also as a prophylactic one (Finkel et al. 1999; Palomaki 1999; Robinson et al. 2000). The findings in this line of research have also been controversial and benefit of antidepressant treatment in recovery from stroke may depend on the identification of specific subgroups of patients and the optimal timing of treatment.

1.4 VASCULAR DEPRESSION

In clinical practice, patients with a first onset of depression in later life are regarded as a specific entity. Age-of-onset as a specific marker was mentioned by Conwell (1989) in the late 1980's. The arbitrary age separating the late from the early-onset subjects was set at 60 years old. The so-called 'late-onset depression' (LOD) is primarily thought to be an organic depression with vascular lesions and neuronal degeneration as major

Table 4: Proposed criteria for Vascular Depression

Cardinal features	1. Clinical and/or laboratory evidence of vascular disease or vascular risk factors. Clinical manifestations may include history of stroke or transient ischemic attacks, focal neurologic signs, atrial fibrillation, angina, history of myocardial infarction, carotid bruit, hypertension and hyperlipidemia. Laboratory findings may include significant white matter hyperintensities at the territory of the perforating arteries, infarcts, or evidence of carotid occlusion or stenosis of the Willis circle arteries
	2. Depression onset after 65 years of age or change in the course of depression after the onset of vascular disease in patients with early–onset depression; development of more frequent and persistent depressive episodes
Secondary features	1. Cognitive impairment consisting of but not limited to disturbance of executive functions, i.e. planning, organizing, sequencing, and abstracting
	2. Psychomotor retardation
	3. Limited depressive ideation, e.g. guilt
	4. Poor insight
	5. Disability
	6. Absence of family history of mood disorders

* The cardinal features are expected in all patients. The secondary features may present in most but not all patients with "vascular depression".

causes (Burvill et al. 1989; Salloway et al. 1996; Holroyd & Duryee 1997). Silent lesions on MRI have frequently been found in elderly subjects with depressive symptoms, without stroke-like symptoms (Fujikawa et al. 1993). Some authors have labelled the (vascular) depressive syndrome a 'pre-stroke depression', suggesting that clinical stroke would soon follow. The concept of vascular depression is actually very old. Around 1900, the German psychiatrist Gaupp already mentioned 'atherosclerotic depression', a concept that was later recognized by Bleuler. The revival of this concept was boosted by the development of new imaging techniques which made it possible to improve the 'golden standard' for the concept of 'vascular depression'. Some called this 'new' group "MRI defined vascular depression", with the vascular lesions on MRI as the obligatory finding (Krishnan et al. 1997). For clinical practice, it would be more useful if these patients could be recognized in daily, routine observation by their clinical characteristics. Some authors have proposed criteria for this vascular depression syndrome (Alexopoulos et al. 1997a; Alexopoulos et al. 1997b). These are outlined in table 4.

1.5 SOURCES OF CONFUSION

1.5.1 Measures of depression

Although depression comprises various symptoms that are traditionally grouped in different clusters, the concept of depression as a single syndrome that represents a final

common pathway, defined by a broad range of biological as well as psychological factors, has become widely accepted in recent decades (Parker 2000). Because of the overlap of both symptomatology and pathophysiology of depression and vascular disease of the brain, renewed discussion has arisen with regard to basic concepts in psychiatry. Especially in subjects in whom a specific cause is presumed, specific clinical profiles may be detected. Until now, most investigators have applied the currently-accepted guidelines and classification, mostly the DSM. This may have hampered the recognition of new, (a)typical forms of PSD. Most authors report 'major' and more prevalent 'minor' depressive disorder, according to DSM-criteria (Eastwood et al. 1989; House et al. 1990). Low mean-scores on the Hamilton Rating Scale for Depression (HAM-D) indeed suggest that it may only concern incomplete or minor depressive states. Clustering of symptoms into specific symptom dimensions may increase the likelihood of an organic, familial and possibly genetic aetiology (Korszun et al. 2004). Some studies have investigated specific neuropsychiatric syndromes caused by stroke. Caplan et al. (1990) studied the behavioural consequences of infarcts involving the caudate nucleus. Cognitive and behavioural abnormalities were frequent, and included abulia, agitation and hyperactivity, contralateral neglect, and language abnormalities. The syndrome of akinetic mutism was found in patients with vascular damage of the frontal lobe or an interruption of the complex frontal subcortical circuits (Nagaratnam et al. 2004). Some authors have focused on individual symptoms of depression and have tried to find correlations with vascular lesion location. Dysphoria as a sign of depression was found to be more frequent in patients with lesions of the parietal and occipital cortex, and 'insomnia' was associated with lesions in the infero-frontal cortex (Stern & Bachman 1991). Emotional indifference is a sign that is often found in patients with a lesion of the non-dominant hemisphere, described by some investigators as the syndrome of aprosodia (Ross 1981).

1.5.2 Temporal relationship

In most studies on the relationship between vascular disease and depression, time course is a varying factor. In some studies, mean-time since stroke varied from six months to more than 10 years. It has been suggested that depression has its major peak prevalence around six months after stroke and that in its natural course it will clear after one year, although follow-up is often incomplete and some patients remain depressed after two years (Robinson et al. 1984b; Robinson et al. 1987). Emery and Oxman (1992) suggested that in late life there is a spectrum of cognitive and affective disorders, including depression, dementia and parkinsonism, which are interrelated. This idea could be transferred to the vascular pathogenesis in the sense that diffuse vascular lesions will give rise to diffuse neuronal degeneration and hence will lead to the same spectrum of cognitive, affective and psychomotor disorders (Steffens et al. 2003).

1.5.3 Study populations

There are major differences in study design and population that influence the results of studies on cerebral vascular disease and depression. Homogeneity of the cohort is one of the major problems. Not only do subjects differ with regard to age at onset, number of previous episodes and duration of the index episode, but they also show variation in type of vascular event and disease-management. Some studies included in-patients in highly specialized, tertiary settings with often complex and refractory symptoms, while other reports are on more 'regularly' referred patients, leading to selection bias. The problem of attrition bias is often encountered in population-based studies. Attrition is selective, usually in the sense that the most severely affected subjects drop out of the study more often than the healthier ones. In studies on the relationship between depression and cerebrovascular disease, selection bias will usually favor a strong relationship, whereas attrition bias works in the opposite direction. Figures on the prevalence of vascular depression and PSD show that, indeed, the highest numbers are found in clinical studies as opposed to population-based studies (Robinson et al. 1984b; Stern & Bachman 1991).

1.5.4 Other etiological factors

Besides the biological and medical consequences of stroke and vascular disease of the brain, there are of course also major psychosocial factors that should be addressed. The sudden loss of functional abilities which will give rise to fears, despair and mourning. The uncertain outcome, with risk of persisting handicap and loss of independence and moreover, the chance of recurrence of (an even more) devastating stroke, can be intimidating. Changes in social roles are inevitable and this may present new problems for patients and their relatives. Premorbid personality traits might be a potential vulnerability factor for the development of PSD (Aben et al. 2002). In the end, PSD and vascular depression are like most psychiatric disorders so-called complex disorders. This means that there will not be a single cause, but a causal chain or number of such causal chains. These interrelated chains may involve genetic, environmental, social and biological risk factors, and none of these factors can be fully understood on its own, but only in the context of all the others. In this thesis, I have made a restriction by focusing on the biological factors.

1.6 AIMS OF THE STUDY AND OUTLINE OF THIS THESIS

The general aim of this study was to identify specific symptom profiles in depressed patients with vascular risk factors and more specifically vascular damage of the brain. A phenomenological approach was chosen because for clinical practice it can be of major significance in detecting depressed subjects with vascular risk-factors, without the use of invasive investigations. Not only may the subsequent recognition of subjects with a

vascular risk contribute to preventing further vascular risks, but the improvement of the psychiatric diagnostic procedure may also lead to an adaptation of treatment strategies and finally to an improvement in the quality of life of subjects with vascular and post-stroke depression.

In this thesis the following questions are addressed:

1. What is the diagnostic value of the HAM-D for subjects who suffered from stroke? Can this instrument be used for the purpose of screening and diagnosis of depression in these patients?
2. Is there a distinct clinical symptom profile of depression for patients who suffer from severe vascular brain disease?
3. Are the affective and cognitive sequelae of vascular brain damage interrelated?
4. Can "vascular depression" be recognized as a distinct entity in the general population based on clinical depressive symptoms?

To answer these questions, data from multiple sources was used. First, a clinical sample of patients was used from a study designed to investigate the role of vascular factors in dementia at the section of Neurovascular Diseases of the Erasmus Medical Center Rotterdam (van Kooten et al. 1998). In this group of patients, a thorough psychiatric work-up was done to determine the co-occurrence of depression and dementia in this post-stroke group. First, we studied the psychometric properties of a frequently-used rating scale for depression, the HAM-D. We compared the psychometric properties for patients who suffered from stroke, Parkinson's and Alzheimer's disease and found out that there might be disease-specific cut-off scores. In the next two chapters, we studied the occurrence of depression in patients who suffer from vascular dementia, describing the clinical profiles of this depressive disorder and looking at the relationship between these patients' affective and cognitive features. A second study on elderly subjects with early dementia and depression is described in chapter 5. This study, using data from the Nijmegen Study on Depression in Dementia also addresses the interrelationship between cognitive and affective features. For chapters six and seven, we have used data from two large, representative samples of community-dwelling elderly persons, the Amsterdam Study of the Elderly (AMSTEL) and the Rotterdam Study (ERGO). The AMSTEL study was a prospective study that started in 1990 and assessed mental health problems, medical diagnoses and demographic characteristics of non-institutional individuals in the 65-84 age bracket who lived in the city of Amsterdam (Schoevers et al. 2000a). The aim of the Rotterdam Study is to investigate determinants of chronic and disabling diseases. The study started in 1990, when all inhabitants 55 years and older of Ommoord, a district of Rotterdam, the Netherlands, were invited to participate. This study is still in progress and has entered its fourth follow-up stage. Alongside mental health and demographic

characteristics, much effort was made in identifying physical disorders, including MRI brain scanning and vascular risk-status in a large subgroup. In both groups, we have investigated the combination of depressive disorder and vascular risk factors, testing the vascular depression hypothesis. In chapter six, we have studied the symptom profiles of depression in subjects with a depressive disorder but with a distinct risk-factor profile. We hypothesized that subjects with a higher vascular risk would show a profile that better fitted the vascular depression hypothesis than those with other somatic risk profiles. In chapter seven, we have tested the proposed criteria for Vascular Depression of Alexopoulos in our two community samples.

Chapter 2

Disease-specific properties of the HAMD in patients with Stroke, Alzheimer's dementia and Parkinson's disease

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2.1 SUMMARY OF CHAPTER 2

To compare the psychometric properties of the HAMD in patients with stroke, Alzheimer's Disease and Parkinson's Disease, receiver operating characteristic (ROC) curves were plotted for each group. The concurrent validity of the HAMD with the DSM-IV criteria for major depressive disorder was high in each of these groups. However, optimal performance of the HAMD requires the application of disease-specific cut-off scores for screening, diagnostic and dichotomization purposes. These disease-specific cut-off scores were highest in PD and lowest in stroke patients, with AD patients falling in-between.

2.2 INTRODUCTION

The Hamilton Rating Scale for Depression (HAMD) is a commonly used instrument in depression assessment and research (Hamilton 1960). In clinical practice, this instrument is of great value to assess the severity of depression in patients suffering from depression without somatic comorbidity. Recently, we have evaluated the validity of the HAMD in patients suffering from Parkinson's disease (PD) (Leentjens et al. 2000). In patients with depressive symptoms and stroke, the validity of the HAMD has not yet been established, although depression rating scales are frequently used in all kinds of research into the prevalence and course of post stroke depression. There are studies in which the validity of the HAMD is established in patients with AD (Vida et al. 1994). Other investigators have employed the HAMD to assess the severity of depressive symptoms in stroke patients and patients with AD, irrespective of the presence of major depression. It has also been used as a diagnostic scale to assess the presence of major depression in stroke and AD patients, and to dichotomize study populations into depressed and non-depressed patients, sometimes to exclude patients from clinical trials (Stern & Bachman 1991). Such use of the HAMD is only justified if there is high concurrent validity with the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) for depressive disorders (APA 1994). In addition, the HAMD score should have high positive and negative predictive value for major depression in these disorders. In patients with PD, the optimal cut-off score for diagnostic purposes was 16/17, meaning that a score of 16 or less indicates the absence of depression and a score of 17 or higher is indicative of the presence of major depression. For screening purposes it was 11/12 (Leentjens et al. 2000). The mean score of non-depressed PD patients was 8.4, which indicates that there might be a disease-specific threshold in this group of patients. In patients with AD the optimal cut-off score was found at 7/8 for diagnostic purposes (Vida et al. 1994).

In order to assess whether disease-specific cut-off scores should be applied for the HAMD in various neurological disorders, we compared the concurrent validity of the HAMD in relation to DSM-IV criteria for major depressive disorder in patients with stroke, AD and PD. Furthermore, we compared the psychometric performance of the HAMD as a screening and diagnostic instrument in these three neurological disorders.

2.3 PATIENTS AND METHODS

Data on the HAMD scores from patients of three different study groups were compared. These groups consisted of patients with stroke, Alzheimer's dementia and Parkinson's disease.

First, HAMD results of 44 stroke patients who were included in the Dutch Vascular Factors in Dementia Study were analyzed. All were in-patients on a neurological ward. Details of the design and characteristics of this study are outlined elsewhere (Van Kooten et al. 1998). Patients with TIA, cerebral infarction or intracerebral hemorrhage were included in this study. Patients with impairment of consciousness or severe aphasia that could preclude valid judgment of cognitive or affective disturbances were excluded. When possible the demented patients, and a random sample of non-demented patients were subjected to a psychiatric evaluation. Only these patients, of whom results on the HAMD were available, were included in this analysis. An indication of cognitive function was achieved using the Mini-Mental State Examination (MMSE) (Folstein et al. 1975). Cognitive function was further assessed between 3 and 9 months after stroke. The diagnosis of dementia was based on the results of an extensive neuropsychological examination, clinical presentation and information from a close relative. A diagnostic panel consisting of two neurologists, a neuropsychologist and a trained physician made a final judgement. For the diagnosis of dementia, the criteria of the DSM-III-R were used (APA 1987). Psychiatric examination was also performed between 3 and 9 months after the stroke. All evaluations were performed in the afternoon to prevent results being influenced by diurnal variations in mood. A DSM-IV diagnosis of major depressive disorder was made using the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott & Spitzer 1978). This is a semi-structured interview, which yielded the 'golden standard' diagnosis of major depression in this group. In addition, all patients, whether depressed or not, underwent a semi-structured interview in which the HAMD was administered.

The second studygroup comprised 85 patients with PD. They were consecutive referrals to the movement disorder clinic of Maastricht University Hospital. They all met the criteria for PD as defined by de United Kingdom PD Society Brain Bank (UK-PDS-BB) (De Rijk et al. 1997). Cognitive function was assessed by the Mini-Mental Status Examination (MMSE). Physical disability was rated according to the Hoehn and Yahr staging system (Hoehn & Yahr 1967). Every patient underwent a protocollised mental status examination. A DSM-IV diagnosis of major depressive disorder was made in a structured interview with the aid of the Structured Clinical Interview for DSM-III-R (SCID-D). This diagnosis was considered the 'golden standard' for major depression in this population (Spitzer et al. 1987). All the patients, depressed and non-depressed, underwent a semi-structured interview to obtain a score on the HAMD. The PD patients who met the DSM-IV criteria for dementia were excluded from further analysis.

The third group comprised 274 patients with AD. These were consecutive referrals to the Maastricht Memory Clinic of Maastricht University Hospital. Dementia was diagnosed according to DSM criteria, while Alzheimer's disease was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders

Table 1: Mean HAMD scores in patients with stroke, AD and PD with and without a depressive disorder

	Mean ± SD (range)	
	Non-depressed	***Depressed***
Stroke	3.6 ± 2.32 [0 – 11]	13.9 ± 4.56 [7 – 24]
Alzheimer's disease	6.9 ± 4.00 [0 – 18]	15.1 ± 4.85 [8 – 26]
Parkinson's disease	8.3 ± 3.87 [1 – 19]	18.1 ± 4.92 [7 – 29]

and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) (McKahnn et al. 1984). The HAMD was used as a symptom checklist to diagnose major depression according to the DSM-IV criteria. The cognitive status of 239 of the patients was also assessed using the MMSE.

2.4 STATISTICAL ANALYSIS

In order to determine and compare the sensitivity and specificity of the HAMD as a diagnostic instrument to diagnose major depression in stroke, AD and PD patients and to obtain optimal cut-off scores, we plotted 'receiver operating characteristic' curves (ROC curves) for the HAMD scores from all three disorders (Murphy et al. 1987). These curves yielded the 'sensitivity' versus '1 minus the specificity' for every possible cut-off point. The optimal cut-off point was determined visually by assessing which score combined maximum sensitivity with optimal specificity. The area under the curve (AUC) is an indicator of the ability of the scale to distinguish between depressed and non-depressed patients. Optimal cut-off scores were determined for each group of patients, including cut-off scores that could be used for a screening, diagnostic and dichotomization (i.e. discriminating depressed from non-depressed patients) purposes. In order to determine whether the HAMD could be used as a predictive test for these three groups of patients, positive predictive (PPV) and negative predictive values (NPV) were calculated for different cut-off scores in the central range of the scale. The three ROC curves were compared in pairs with the Hosmer-Lemeshow goodness-of-fit test (Hosmer et al. 1988). All analyses were performed with the Stata software package, release 5 (StataCorp 1997, College station, Texas/USA) .

2.5 RESULTS

The average age in the PD group was lower than that in the other two groups: stroke patients 70.3 years (SD 16.2), AD patients 71.1 years (SD 8.8) and PD patients 67.3 years (SD 10.2). Although this reached statistical significance, this difference in age does not,

in our opinion, reflect any clinical relevance. The group of AD patients contained significantly more women than the other two groups: stroke patients 36.4%, AD patients 59.5% and PD patients 40.0% (chi-square = 15.278, df 2, p < .001).

Mean scores on the MMSE for stroke patients, AD patients and PD patients were 19.18 (SD 6.87, range 9–30), 18,96 (SD 5.80, range 0–29) and 27.76 (SD 1.82, range 23–30).

Twenty-three of the stroke patients fulfilled criteria for dementia (52%). The PD patients had the following Hoehn and Yahr classifications: 8 stage I, 56 stage II, 17 stage III, 4 stage IV and none stage V.

The prevalence of major depressive disorder was highest in the stroke group: 34.1%. In the AD group the prevalence was 22.6%, while in the PD group it was 23.5%. This difference did not reach statistical significance (chi-square = 2.743, df 2, p = 0.254).

Mean HAMD scores, ranges and standard deviations (SD) are listed in table 1 for the depressed and the non-depressed subgroups in each disorder. Frequency distribution

Table 2a: Stroke (N=44). Sensitivity, specificity, positive and negative predictive values at different cut-off scores for the 17 item Hamilton Rating Scale for Depression (PPV=positive predictive value, NPV=negative predictive value, *=maximum sensitivity and specificity)

Cut-off	**4/5**	**5/6***	**6/7**	**7/8**	**8/9**	**9/10**	**10/11**
Sensitivity	1.00	1.00	0.93	0.93	0.87	0.73	0.73
Specificity	0.86	0.93	0.93	0.93	0.97	0.97	1.00
PPV	0.79	0.88	0.88	0.88	0.93	0.92	1.00
NPV	1.00	1.00	0.96	0.96	0.93	0.88	0.88

Table 2b: Alzheimer (N=243). Sensitivity, specificity, positive and negative predictive values at different cut-off scores for the 17 item Hamilton Rating Scale for Depression (PPV=positive predictive value, NPV=negative predictive value, *=maximum sensitivity and specificity)

Cut-off	**6/7**	**7/8**	**8/9**	**9/10***	**10/11**	**11/12**	**12/13**	**13/14**
Sensitivity	1.00	0.95	0.90	0.86	0.77	0.68	0.52	0.45
Specificity	0.64	0.71	0.79	0.84	0.90	0.92	0.95	0.96
PPV	0.45	0.49	0.55	0.61	0.69	0.71	0.74	0.76
NPV	1.00	0.98	0.97	0.95	0.93	0.91	0.87	0.86

Table 2c: Parkinson (N=85). Sensitivity, specificity, positive and negative predictive values at different cut-off scores for the 17 item Hamilton Rating Scale for Depression (PPV=positive predictive value, NPV=negative predictive value, *=maximum sensitivity and specificity)

Cut-off	**9/10**	**10/11**	**11/12**	**12/13***	**13/14**	**14/15**	**15/16**	**16/17**
Sensitivity	0.95	0.85	0.80	0.80	0.75	0.70	0.70	0.60
Specificity	0.72	0.79	0.85	0.92	0.92	0.96	0.99	0.99
PPV	0.51	0.55	0.62	0.76	0.75	0.82	0.93	0.92
NPV	0.98	0.94	0.93	0.94	0.92	0.91	0.91	0.89

analysis showed that there were no missing scores in the central score range of the HAMD in the three groups of patients.

Sensitivity, specificity, PPVs and NPVs for different cut-off scores of the HAMD are shown in tables 2a-c for the patients with stroke, AD and PD, respectively. ROC curves for the three groups of patients are shown in the figures 1-3, respectively.

The cut-off score for maximum discrimination (dichotomization) between depressed and non-depressed patients could be determined visually from the ROC curves as the point at which the highest sum of sensitivity and specificity was reached. In the stroke group this point was reached at a cut-off score of 5/6 (sensitivity 1.00, specificity 0.93), in the AD group at 9/10 (sensitivity 0.86, specificity 0.84) and in the PD group at 12/13 (sensitivity 0.80, specificity 0.92). The AUC was large in all three groups of patients, which indicates that the HAMD score has high concurrent validity with the DSM-IV criteria for major depressive disorder in these diseases. To be useful for diagnostic purposes, an instrument needs a combination of high specificity and high PPV; this yielded higher cut-off points than those for dichotomization. Once again there were differences between the three groups: Optimal cut-off for diagnostic purpose was found in the stroke group at 10/11 (specificity 1.00, PPV 1.00). In the AD group, the optimal diagnostic cut-off point was found at 13/14 (specificity 0.96, PPV 0.76). In the PD group the point was found at 15/16 (specificity 0.99, PPV 0.93). To be useful for screening purposes an instrument needs a combination of high sensitivity and high NPV. These requirements were met in all three groups of patients at low cut-off scores. This cut-off point was lowest in the stroke group: 5/6 (sensitivity 1.00, NPV 1.00). In the AD group, the optimal cut-off point was found at 6/7 (sensitivity 1.00, NPV 1.00) and in the PD group at 9/10 (sensitivity 0.95, NPV 0.98). Further 'goodness-of-fit' analyses of the ROC curves revealed statistically significant differences between the three groups.

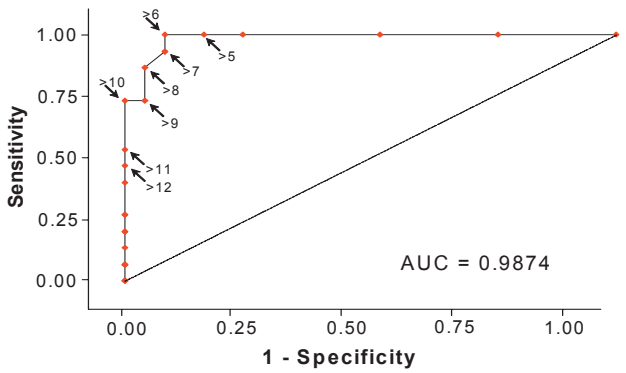

Figure 1: Receiver Operating Characteristic (ROC) curve for the HAMD in patients with stroke (AUC = Area Under Curve)

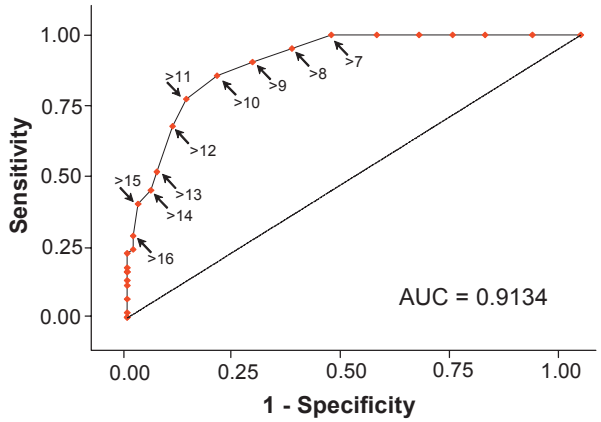

Figure 2: Receiver Operating Characteristic (ROC) curve for the HAMD in patients with Alzheimer disease (AUC = Area Under Curve)

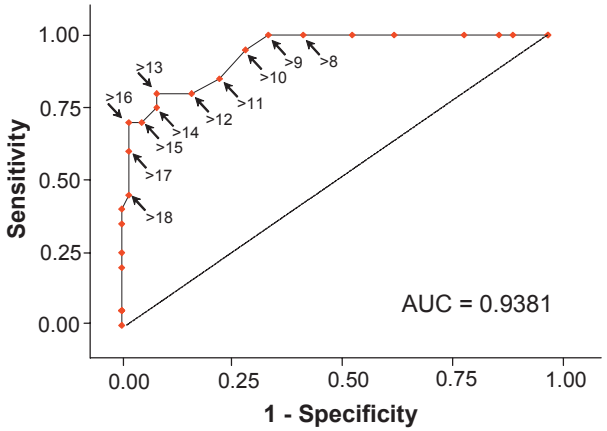

Figure 3: Receiver Operating Characteristic (ROC) curve for the HAMD in patients with Parkinson's disease (AUC = Area Under Curve)

2.6 DISCUSSION

In this study we showed that the concurrent validity of the HAMD for DSM-IV major depression in stroke, AD and PD was high. However, optimal performance requires that different cut-off points are taken into consideration for each organic disorder. The prevalence of major depression in our three groups was comparable with that reported by others (Robinson 1997; Cummings 1992; Forsell & Winblad 1998). In agreement with our previous study on patients with PD (Leentjens 2000), in the present study, the non-depressed patients with stroke and AD had higher scores than non-depressed 'normal' individuals; the PD patients in our analyses had the highest scores. At low disease

specific cut-off points, the HAMD can be used as a screening tool in all three disorders. However, other, easier to administer self-report questionnaires may be more practical for this purpose as they do not require trained personnel. At higher cut-off scores, the HAMD also proved to be useful as a diagnostic tool, with an optimum cut-off point of 10/11 for stroke, 13/14 for AD and 15/16 for PD. There was no significant difference in performance of the HAMD between the three organic disorders, when the disease-specific cut-off scores were used. As we described in the methods section, the stroke group consisted of demented 'cases' and non-demented 'controls'. Therefore, dementia was present in half of the stroke patients, whereas in stroke populations, the prevalence of dementia has been reported to be approximately 25% (Van Kooten et al. 1998; Tatemichi et al. 1993). Nevertheless our findings indicate that different organic disorders are associated with different profiles of clinical mood syndromes. This is important, because the previously established cut-off scores for 'healthy individuals' did not apply to our three groups of patients. When for example a clinical trial on the efficacy of antidepressants is conducted on patients with these disorders, adjusted cut-off's should be taken into account when selecting end-points to determine improvement during or after therapy. It is probably because of the somatic and psychomotor items that the floor score of the HAMD is higher in depressed patients with an organic disorder than in those without.

Criticism could be given on the fact that we used data out of three different studies and obtained psychiatric diagnosis in a different way in these three studies. Although this is true we think that applying DSM-IV criteria to all three groups in a uniform way has minimalised the influence of this methodological shortcoming. Next, some concerns could be expressed on the problem of diagnosing depression in a group of patients with dementia. Although this is true, others have recently shown that depressive symptoms can be reliably scored with the HAMD in patients with AD and that they are significantly related to an underlying depressed mood (Chemerinski et al. 2001). Another problem in studies such as this is that there is no solid 'golden standard' for psychiatric disorders. Because of the psychomotor and autonomous symptoms that accompany organic brain disease it may be easier to come to the DSM diagnosis of "major depressive disorder" in these patients. However, until now there is no suitable alternative for a 'golden standard' diagnosis of depression. In theory it is possible for patients with an organic brain disorder to have a high score on the HAMD, without showing any of the core symptoms of major depression. The high concurrent validity of the HAMD with the DSM-IV criteria for major depression showed that although this is theoretically possible, it is not a major clinical concern. Finally, we suggest that our findings have to be validated with the results of other cohorts of patients with stroke, AD, and PD.

2.7 CONCLUSION

The concurrent validity of the HAMD with the DSM-IV diagnosis of major depressive disorder is high for patients with stroke, AD and PD. However, optimal performance requires the use of disease-specific cut-off points for screening, diagnostic and dichotomization purposes. Both in clinical practice and in research design it is essential to take these disease-specific qualities of the HAMD into account. These disease-specific qualities should be established in other and preferable larger cohorts.

Chapter 3

Depression in post-stroke dementia

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3.1 SUMMARY OF CHAPTER 3

After a stroke, cognitive, affective and behavioural disturbances are common. It has been suggested that the nature of affective symptomatology can help to differentiate organic from psychological depression. To study the presence of different dimensions of depression in subjects with vascular dementia, cognitive and affective symptoms were assessed in 78 stroke patients and a principal component analysis was performed on these symptoms. Also, a discriminant analysis was carried out to establish the contribution of different symptoms on the diagnosis 'depressive disorder' and 'dementia'. The principal component analysis revealed three distinct sub-syndromes: one with predominantly mood symptoms, one with essentially psychomotor symptoms, and one with vegetative symptoms. Mood, psychomotor and vegetative symptoms were all independently and strongly related to a diagnosis of major depressive disorder according to DSM-III-R criteria. The psychomotor factor was also firmly associated with dementia.

Discriminant analysis gave further support for our conclusion that some of the depressive features, in particular the psychomotor factor, are at least partly related to the organic brain damage from stroke.

The results indicate that different dimensions of depression could be discerned in a group of stroke patients and that the symptom profile of depression in these patients can be affected by the presence of dementia.

3.2 INTRODUCTION

A variety of cognitive, affective and behavioural disturbances may be present in patients after a stroke (Sharpe et al. 1990; Tatemichi et al. 1993). These disturbances, however, are not always recognised, and if so, often not correctly diagnosed. This may lead to difficulties during the rehabilitation process (Kotila et al. 1999). Furthermore these cognitive, affective and behavioural disturbances after stroke have complex relationships with each other, and cognitive dysfunction cannot be assessed properly without paying attention to the affective and behavioural symptoms.

Both psychological factors, such as loss of function and mobility and changes in interpersonal relationships, and neurobiological brain changes may give rise to cognitive disturbances and symptoms of depression. Since it may have major implications for treatment, it is important to know whether cognitive and depressive symptoms have a predominantly psychological or neurobiological origin. It has been suggested from an epidemiological study that the nature of depressive symptomatology can help to differentiate organic from psychological depression. In this study, patients with a probable major organic aetiology for their depression showed a syndrome with the key symptoms irritability, psychomotor retardation, confusion and suicidal ideation (Oyen 1995). Also, Forsell demonstrated a subdivision of depression in the elderly, describing 'low motivation' and 'low mood' syndromes. Patients with predominantly 'motivational' symptoms more likely had an organic etiology for their depression (Forsell et al. 1993). Others replicated this finding (Janzing et al. 1999). Thus, the symptom profile in stroke patients may be an indication of the involvement and relevance of an organic lesion for the depression.

In the present study we investigated whether subdivision of depressive disorder into different dimensions would differentiate between post stroke depression and dementia. We therefore compared depressive symptoms of stroke patients with and without dementia. Furthermore, we studied the contribution of individual depressive symptoms to a diagnosis of major depressive disorder in this patient population.

3.3 METHODS

3.3.1 Subjects

The subjects were recruited from the Rotterdam Stroke Databank (RSD), a prospective registry of patients with a transient ischaemic attack (TIA), cerebral infarction, or primary intracerebral haemorrhage that were admitted to the department of Neurology of the University Hospital Rotterdam. From March 1, 1993, until January 15, 1996, all consecutive patients who met the criteria for enrolment in the Dutch Vascular factors in Dementia

Study were included. Characteristics of the design and demographic variables of this study are outlined in detail elsewhere (Van Kooten et al. 1998). In short, patients had to be 55 years or older and to have had a TIA with neurological signs on examination, a cerebral infarction, or intracerebral haemorrhage. Patients were excluded when a reliable assessment of dementia could not be made because of aphasia (i.e., a score of less than 3 on the Aphasia Severity Rating Scale from the Boston Diagnostic Aphasia Examination) (Goodglass and Kaplan 1983), severe sensory handicaps (e.g., deafness or blindness), persistent impairment in consciousness, a history of severe psychiatric symptoms other than mood disturbances, or insufficient command of the Dutch language. Additional reasons for exclusion were concomitant primary cerebral disorders, or severe co-morbidity with a short life expectancy. Informed consent according to institutional guidelines was obtained from all patients or from close relatives in case of impaired judgement in the patient. The "golden standard" diagnosis of dementia was based on the results of an extensive neuropsychological examination, clinical presentation and information from a close relative. A diagnostic panel consisting of two neurologists, a neuropsychologist and a trained physician made a final judgement. All demented patients were scheduled for psychiatric examination. For the diagnosis of dementia, the criteria of the DSM-III-R were used (APA 1987). In addition, a group of control patients randomly selected from the patients who did not fulfil the criteria for dementia was subjected to the same psychiatric evaluation.

3.3.2 Cognitive evaluation

During hospital admission, an interview with a close relative and the score on the Blessed Dementia Scale (BDS) established premorbid cognitive functioning (Katzman et al. 1983). Education was categorised by the number of years of schooling completed. Between 3 and 9 months after stroke onset, a neurologist assessed cognitive function, based on clinical observation, the information of a close relative, and the score on the BDS. In case of any suspicion of cognitive decline, patients were invited for an extensive neuropsychological examination, which is outlined in detail elsewhere (De Koning et al. 1998).

3.3.3 Psychiatric evaluation

All psychiatric evaluations were performed in the afternoon to prevent results being influenced by diurnal variations in mood. Detailed information concerning former depressive or other psychiatric episodes was obtained through an interview with the patients and/or their family or the general practitioner.

A DSM psychiatric diagnosis of major depressive disorder (MDD) was established with the affective part of the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott & Spitzer 1978). This is a semi-structured interview, which not only may confirm the diagnosis of major depressive disorder according to DSM-IV-criteria (APA 1994),

but also sheds light on milder depressive symptomatology, with emphasis on dimensional instead of syndromal properties. Symptoms were dichotomised into 'absent' or 'present'.

3.3.4 Statistical analysis

For statistical analysis we used the Statistical Package for the Social Sciences (SPSS) for Windows version 9.0. Chi-square analysis was used to compare categorical variables and the independent samples t-test to compare continuous variables. A principal component analysis with varimax rotation was carried out on all depressive symptoms of the SADS with prevalence above 10%. Symptoms were added to a factor when factor loading was greater than .40. For all factors internal consistency was determined using Cronbach's α. The associations between the factor-scores on the one hand and major depression, dementia and the combination of major depression and dementia on the other hand, were studied using logistic regression analysis. Next, a discriminant analysis was carried out on the basis of the individual items of the SADS. A model was calculated to predict whether patients would fall into the depressed or the non-depressed group according to the golden standard, i.e. the DSM-criteria. Next, a correlation coefficient with this discriminant function was obtained for each SADS-item and these were grouped in order of descending correlation coefficients, i.e. in order of decreasing sensitivity. Wilk's lambda was calculated as a test of discriminant function. The correlation coefficients reflect the relative contribution of these items to a diagnosis of MDD.

3.4 RESULTS

3.4.1 Procedure

In 83 out of 300 patients, there was a clinical suspicion of dementia. After an extended neuropsychological evaluation, 71 of them were diagnosed as demented. Fifty-four of these patients underwent psychiatric evaluation. In 6 patients, psychiatric evaluation could not take place because they died between cognitive evaluation and the scheduled psychiatric examination. In the other 11 patients, the severity of the dementia syndrome prevented a reliable psychiatric evaluation. Of the 217 patients without clinical suspicion of dementia, a sample of 24 patients was drawn. Thus, a total of 78 patients were included in the present study. Psychiatric evaluation was performed between 6 and 24 months after the stroke.

3.4.2 Assessment of affective symptoms

Affective assessment of demented and non-demented stroke patients revealed four different groups: A group of 33 patients who were classified as having dementia but no major depression. A second group meeting criteria for a major depressive disorder but

Table 1: Patient characteristics

	Dementia N = 54	No dementia N = 24	P-value
Age	74.3 (7.7)	69.5 (7.7)	**0.013**
Years of education (mean)	7.2 (3.1)	8.8 (2.2)	**0.029**
Female sex	29 (54)	8 (33)	0.078
MMSE	18.7 (6.8)	27.5 (1.9)	**< 0.001**
Depression:			
Major depression	21 (39)	7 (29)	0.287
Minor depression	10 (18)	4 (17)	0.559

MMSE = MiniMentalStateExamination
numbers in brackets indicate SD (means) or percentage (prevalence)
P – values: unpaired t-test with continues variables, Fisher's exact-test with nominal variables. Significant p-values are printed in bold

not for dementia, consisting of 7 patients. A group of patients who met criteria for both major depressive disorder and dementia, consisting of 21 patients and finally a group of 17 patients who did not meet any criteria for depressive disorder nor for dementia. The clinical characteristics of the demented and non-demented patients are shown in table 1. The frequency of major and minor depression did not differ significantly between the demented and the non-demented group. Twenty-eight (36%) patients had a major depression according to DSM-IV criteria. An additional 14 (18%) patients fulfilled criteria for a minor depression. The frequencies of the different depressive symptoms of the SADS for both demented and non-demented patients were assessed and symptoms with a frequency of less than 10% were excluded from further analysis. These symptoms were: depersonalisation, feelings of guilt, hallucinations, hypochondriasis, increase of appetite, obsessions, panic attacks, paranoid thinking, self-dismay and weight increase.

3.4.3 Principal component analysis

A principal component analysis was carried out using symptoms with a minimum prevalence of 10% in at least one of both groups, which resulted in six factors (table 2, all subjects). The fifth and sixth factors only consisted of one or two symptoms and were therefore excluded from further evaluation. Symptoms on the first factor, accounting for 29.9% of the variance, appeared to belong to the "mood" dimension of depression. The second factor concerned "psychomotor" symptoms and the third factor seemed to represent the "vegetative" dimension of depression. Both the second and third factor explained 8.5% of the variance. Anxiety had a high loading both on the first and the fourth factor. The symptoms "diminished interest and pleasure" and "insomnia" had a high loading on two of the factors and were excluded from further analysis because of lack of specificity. The test on internal consistency of the first four factors (consisting of three

or more symptoms) revealed Cronbach's α's greater than .70 for the first three factors (.86, .72, and .70) and .58 for the fourth factor. Therefore the fourth factor was excluded from further analyses. A factor sum-score for each factor was calculated by adding one point for each symptom present. Mean factor scores were calculated for demented and non-demented stroke patients and are outlined in table 3. The only significant difference was found for the psychomotor factor, which showed a higher mean factor sum score in the demented subgroup.

3.4.4 Discriminant analysis

The results of the discriminant analysis for a diagnosis of MDD are shown in table 4. Wilks' lambda for this model was highly significant ($\Lambda = 0.153$, chi-square =124.71, df =19, $p < 0.001$). In this model 98% of the patients were correctly classified as depressed

Table 2: principal component analysis of depressive symptoms. Rotated component matrix.

	"mood"	**"psychomotor"**	**"vegetative"**			
	I	II	III	IV	V	VI
Agitation	.02	-.10	-.04	.16	-.05	**.86**
Anger	**.66**	.04	.09	-.24	-.13	.00
Anxiety	**.42**	.04	-.14	**.42**	**-.51**	-.03
Diminished interest and pleasure	**.42**	.17	**.42**	.32	.13	.11
Depressed mood	**.66**	.29	.34	.20	.01	-.06
Increased sleeping at daytime	.08	.06	-.07	.14	**.83**	-.09
Indecisiveness	-.09	-.01	.12	**.65**	.30	.22
Insomnia	.06	**.52**	**.42**	.03	-.35	.36
Loss of appetite	.21	.16	**.84**	-.11	-.04	.01
Loss of energy	.18	**.80**	.06	-.07	-.02	.01
Negative thoughts	**.55**	.20	.17	-.08	.36	.30
No expectations of the future	**.74**	.13	.11	.38	.11	.10
Observed depression	.37	**.61**	.20	.35	.12	.06
Psychomotor retardation	.28	**.70**	-.02	.31	.21	-.26
Ruminations	**.76**	.29	.21	.07	-.11	-.08
Self-pity	**.70**	.08	.07	-.04	-.08	-.11
Social withdrawal	**.60**	.03	.11	.38	.12	-.22
Suicidal thoughts	**.59**	.23	-.18	.06	-.03	.16
Thinking/concentration disturbances	.11	.20	.08	**.79**	-.15	.04
Weight loss	.05	-.05	**.83**	.25	.02	-.08
Cronbach's α	.86	.72	.70	.58	–	–

Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization. Only symptoms with a prevalence greater than 10% were included in the analysis. Factor loadings < -.40 and > .40 are printed in bold

Table 3: Mean factor sum-scores for demented and non-demented stroke patients

	Dementia	*No-dementia*	*P-value*
Mood factor	2.06 (2.19)	1.75 (2.61)	0.594
Psychomotor factor	1.59 (1.24)	0.96 (1.04)	**0.032**
Vegetative factor	0.39 (0.71)	0.33 (0.64)	0.744

Numbers in brackets indicate SD; t-test; Significant p-value printed in bold.

or non-depressed. As to be expected, of all the SADS-items, the key-features of MDD, depressed mood and loss of interest, were the best discriminators between depressed and non-depressed patients. Somatic items, such as loss of appetite and weight, insomnia and thinking/concentration disturbances, had low discriminative properties.

3.5 DISCUSSION

To find out whether subdivision of depressive disorder into different dimensions would differentiate between post stroke depression and dementia, we compared depressive symptoms in a group of stroke patients with and without dementia. Three important depressive dimensions were found: First, a "mood" one, consisting of depressed mood, anger, negative and suicidal thoughts, ruminations and social withdrawal. A second, psychomotor, dimension consisted of psychomotor retardation, observed depression and loss of energy. The third, vegetative dimension consisted of weight and appetite loss. Using multiple logistic regression, it was found that all three factors were associated to the DSM-diagnosis "major depressive disorder" in these post-stroke patients. The psychomotor dimension was also firmly associated with a diagnosis of "dementia", in contrast to the other two dimensions.

These findings support the notion that some of the depressive features, in particular the psychomotor ones, are at least partly due to the organic brain damage from stroke. Comorbid psychological depression will give rise to more and other depressive symptoms, as represented in the mood and vegetative dimensions.

In our study-group, the core symptoms of major depression, depressed mood, loss of interest, and no expectations of the future, are most sensitive in predicting a depressive disorder. Symptoms such as psychomotor retardation, observed depression and thinking/concentration disturbances appeared to be sensitive predictors of both depressive disorder and dementia, and will therefore give rise to difficulties in clinical decision making. Finally, vegetative depressive symptoms, such as insomnia and loss of appetite are common in depressed as well as in non-depressed patients with vascular dementia.

Table 4: Structure matrix of SADS items, grouped in descending order of correlation within the discriminant function. Depressive disorder.

Item	*Correlation coefficient*
Depressed mood	.55
Loss of interest	.40
Ruminations	.37
No expectations of the future	.33
Observed depression	.33
Psychomotor retardation	.26
Social withdrawal	.25
Negative thoughts	.24
Suicidal thoughts	.22
Self pity	.22
Loss of weight	.21
Loss of energy	.21
Loss of appetite	.20
Insomnia	.18
Anger	.18
Thinking/concentration disturbance	.14
Indecisiveness	.05
Increased sleeping	-.04
Agitation	-.01

Our results of the principal component analysis are consistent with those found by Forsell and Janzing, although the components of our dimensions differ in some aspects (Forsell et al. 1993; Janzing et al. 1999). These differences in symptom profiles can be attributed to various factors. In contrast to our patients, Janzing and Forsell studied subjects who were living in the community and showed a low prevalence of major depressive disorder, whereas our study group was a clinical sample of patients who had recently suffered a stroke, were predominantly demented and had a high prevalence of major depression. Moreover, there is an important difference in diagnostic instruments used. Furthermore, we counted all depressive symptoms analyzing only those that had a prevalence of 10% or higher, whereas Forsell and Janzing performed their analyses only with the nine symptoms of the DSM-criteria, irrespective of the frequency of their occurrence. Finally, we included each factor with an acceptable internal consistency, whereas Forsell and Janzing extracted only two factors.

There are some shortcomings to be noticed in our study. First, a sufficient control-group of patients with a stroke but without dementia is lacking. This could have a major

influence on our outcome and so a new study with an accurate control group is needed to replicate our findings. Other important limitations include the modest group size (type-2 error) and the cross-sectional design.

It should be emphasised that the prevalence of dementia in general in stroke populations is only twenty-five percent (Tatemichi et al. 1993). As far as we know, this is the first principal component analysis of depressive symptomatology in patients with vascular dementia.

Subdivision of depression into mood, psychomotor and vegetative dimensions may be useful in predicting the course of depressive disorders in patients with vascular dementia and their impact on the rehabilitation process.

However, further investigations are necessary to confirm our findings. Clinical, biochemical and radiological markers of the mood, psychomotor and vegetative dimensions could be of great help in unravelling the clinical problem of post stroke dementia and mood disorders in other brain diseases. Finally, both drug and psychotherapeutic clinical trials may elucidate whether these interventions are beneficial for subgroups of patients with post stroke dementia or depression.

Chapter 4

Post-stroke dementia and depression: fronto-subcortical dysfunction as missing link?

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Submitted for publication

4.1 SUMMARY OF CHAPTER 4

To test the hypothesis that depressive symptoms in dementia reflect dysfunction in fronto-subcortical pathways, associations were computed between measures of depressive symptoms and a comprehensive set of neuropsychological tests in a sample of fifty-four subjects with a post-stroke dementia. Our hypothesis was supported by a negative correlation between scores on the Verbal Fluency Test and the total numbers of motivational depressive symptoms. None of the neuropsychological tests was significantly related to the number of mood symptoms neither did they correlate with the total number of depressive symptoms. This study gives further evidence for the assumption that motivational-based depressive symptoms partially originate from fronto-subcortical dysfunction.

4.2 INTRODUCTION

Both depression and dementia frequently complicate the clinical course of stroke. Syndromal or subsyndromal depression occurs in about 40% (Sharpe et al. 1990) and dementia in approximately 25% of patients with a recent stroke (Tatemichi et al. 1990; van Kooten & Koudstaal 1998). Although little research has been done on the combination of 'vascular' or 'post-stroke' dementia and 'vascular' or 'post-stroke' depression, it is evident from clinical practice that there is a major overlap of the cognitive and affective symptoms that occur after stroke. Earlier studies on the symptoms of depression in Alzheimer's (AD) and Post-stroke Dementia suggested two distinct dimensions: (Forsell et al. 1993; Janzing et al. 1999a; Naarding et al. 2003)

(a) A factor of mood disturbance consisting of the symptoms dysphoria, feelings of guilt, thoughts of death and appetite disturbance.
(b) A factor of motivational disturbance containing the symptoms loss of interest, psychomotor change, loss of energy and thinking or concentration disturbance.

Studies in dementia, Parkinson's disease and normal aging have suggested that motivational depressive symptoms reflect disturbances in fronto-subcortical circuits. In subjects with Parkinson's disease most of the motivational symptoms, but none of the mood symptoms fluctuated with changes in other Parkinson's symptoms or ameliorated on dopaminergic medication (Hoogendijk et al. 1998). In normal high-functioning elderly, motivational symptoms, but not mood symptoms were found to be associated with MRI deep white matter hyperintensities (Nebes et al. 2001). In a former presentation of our findings on the phenomenology of depression in patients with post stroke dementia, we demonstrated that only the motivational symptoms in this group correlated with the presence of dementia (Naarding et al. 2003). Former studies have demonstrated that the location of the vascular lesion correlates with the presence and severity of depressive symptoms. Depressive disorder is found to be more frequent and more severe with more frontal positioning of the vascular lesion in patients with a post stroke depression (Robinson et al. 1984a). Although this finding is still controversial (Carson et al. 2000), it would be in line with the assumption that fronto-subcortical dysfunction gives rise to motivational depressive symptoms. Consequently, one would expect that these fronto-subcortical disturbances were reflected in disturbances in performance on frontal tasks in neuropsychological examinations. In a recent study we found neuropsychological support for the relationship between motivational symptoms and fronto-subcortical disturbance in residents of an elderly home with cognitive dysfunction (Janzing et al. chapter 5 this thesis). Subdivision of depressive features that are the direct result of the neuro-degenerative or neurovascular damage and features that are the result of the psychological impact of the disease and handicap could be of use for everyday clinical

management. So far, treatment is similar for post stroke and idiopathic depression, but possibly some signs and symptoms would make a certain treatment regime preferable.

In the present study, we investigated the relationship between motivational symptoms of depression and fronto-subcortical dysfunction in 54 patients with post stroke dementia.

4.3 METHODS

4.3.1 Subjects and procedure

The subjects were recruited from the Rotterdam Stroke Databank (RSD), a prospective registry of patients with a transient ischemic attack (TIA), cerebral infarction, or primary intracerebral hemorrhage who were admitted to the department of Neurology of the University Hospital Rotterdam. From March 1, 1993, until January 15, 1996, all consecutive patients who met the criteria for enrolment in the Dutch Vascular factors in Dementia Study were included. Characteristics of the design and demographic variables of this study are outlined in detail elsewhere (Van Kooten et al. 1998). In short, patients had to be 55 years or older and to have had a TIA with neurological signs on examination, a cerebral infarction, or intracerebral hemorrhage. Patients were excluded when a reliable assessment of dementia could not be made because of aphasia (i.e., a score of less than 3 on the Aphasia Severity Rating Scale from the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan 1983)), severe sensory handicaps (e.g., deafness or blindness), persistent impairment in consciousness, a history of severe psychiatric symptoms other than mood disturbances, or insufficient command of the Dutch language. Additional reasons for exclusion were concomitant primary cerebral disorders, or severe co-morbidity with a short life expectancy. Informed consent according to institutional guidelines was obtained from all patients or from close relatives in case of impaired judgment in the patient. The "golden standard" diagnosis of dementia was based on the results of an extensive neuropsychological examination, clinical presentation and information from a close relative. A diagnostic panel consisting of two neurologists, a neuropsychologist and a trained physician made a final judgment. All demented patients were scheduled for psychiatric examination. For the diagnosis of dementia, the criteria of the Diagnostic and Statistical Manual of Mental Disorders, third edition, Revised, (DSM-III-R) were used (APA 1987).

Figure 1 is a schematic representation of the diagnostic procedure. In 83 out of 300 consecutive admissions of patients with a TIA, cerebral infarction or primary intracerebral hemorrhage, there was a clinical suspicion of dementia. After an extended neuropsychological evaluation, 71 of these were diagnosed as demented. In 6 patients, psychiatric evaluation could not take place because they died between cognitive evaluation

and the scheduled psychiatric examination. In the other 11 patients, the severity of the dementia syndrome prevented a reliable psychiatric evaluation. Thus, a total of fifty-four patients underwent an extensive psychiatric evaluation between 6 and 24 months after the stroke.

4.3.2 Cognitive evaluation

During hospital admission, an interview with a close relative and the score on the Blessed Dementia Scale (BDS) established premorbid cognitive functioning (Katzman et al. 1983). Education was categorized by the number of years of schooling completed. Between 3 and 9 months after stroke onset, a neurologist assessed cognitive function, based on clinical observation, the information of a close relative, and the score on the BDS. In case of any suspicion of cognitive decline, patients were invited for an extensive neuropsychological examination, which consisted of the following:

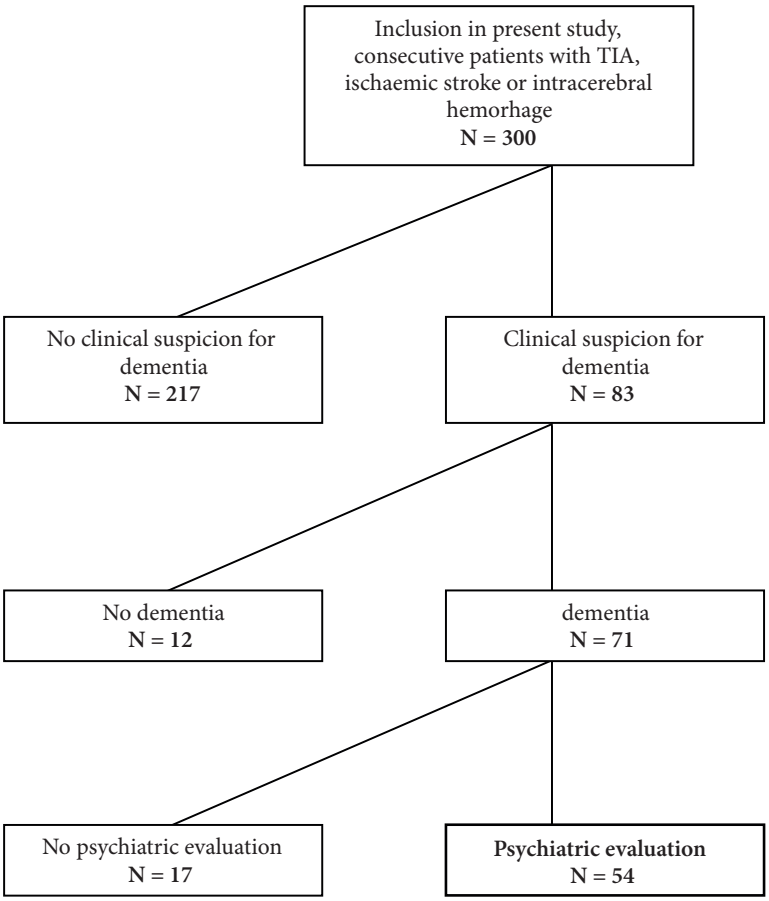

Figure 1: Schematic representation of the diagnostic procedure

1. An intelligence test (either the shortened version of the Groninger Intelligence Test, (Luteijn & Vanderploeg 1983) a Dutch intelligence test, or when this could not be administered, Raven's Colored Matrices, a non-verbal test (Raven 1965)).
2. Word-finding difficulties were examined with the shortened form of the Boston Naming Test (the Consortium to Establish a Registry for Alzheimer's Disease [CERAD] (Morris et al. 1989)).
3. Memory was evaluated with the Word List Memory (CERAD/Morris et al. 1989) and the Rivermead Behavioral Memory Test (Wilson et al. 1985).
4. Immediate verbal recall and attentional capacity were measured using Digit Span forward and backward (Wechsler Adult Intelligence Scale [WAIS] (Wechsler & Stone 1955))
5. Frontal, executive functioning was measured with the Verbal Fluency Test (VFT, animals, occupations and letter B), Stroop color word test part III and Trail-Making Test B (Hammes 1978; Reitlan 1958).
6. Visuoconstructive ability was measured by copying the drawing of a circle, diamond, two overlapping rectangles, and a cube (CERAD/Morris et al. 1989).

A final judgment of cognitive functioning was made by a diagnostic panel consisting of two neurologists, a neuropsychologist and a trained physician. Criteria of the DSM-III-R were used (APA 1987). Further sub-classification of dementia took place according to the research criteria of the NINDS-AIREN international workshop (Roman et al. 1993).

When tests could not be administered and we were confronted with missing values we distinguished between missing values due to cognitive or behavioral disturbances and missing values due to other reasons. This latter category included communication and logistic problems. The majority of specific tests on executive functioning or "frontal" tests were not administrable in demented patients due to cognitive disturbances. We therefore included only the scores on semantic and phonological fluency, as measures of executive functioning in our analyses.

4.3.3 Psychiatric evaluation

All psychiatric evaluations were performed in the afternoon to prevent results being influenced by diurnal variations in mood. Detailed information concerning former depressive or other psychiatric episodes was obtained through an interview with the patients and/or their family or the general practitioner.

A semi-structured interview - the affective part of the Schedule for Affective Disorders and Schizophrenia (SADS) - was used to elucidate all depressive symptoms (Endicott & Spitzer 1978). With this instrument, a DSM-IV psychiatric diagnosis of major depressive disorder (MDD) could be made (APA 1994).

Moreover, symptoms were dichotomized into 'absent' or 'present'. For each individual the following measures of depression were computed by counting the positively rated criteria.

- Depressive symptoms (all criteria of major depressive episode according to DSM-IV).
- Mood symptoms (dysphoria, appetite disturbance, feelings of guilt and thoughts of death).
- Motivational symptoms (loss of interest, psychomotor change, loss of energy and thinking or concentration disturbance).

4.3.4 Statistical analysis

For statistical analysis we used the Statistical Package for the Social Sciences (SPSS) for Windows version 10.0. For all test scores, means (SD) were calculated. Next, we replaced each missing value due to cognitive/behavioral disturbances by the worst performance in this study group on that particular test (Smeding & De Koning 2000). After this adjustment, we calculated means (SD) of the adjusted scores. To determine the effect of these adjustments, we computed the effect sizes of each test variable. The effect size can be calculated by the difference between the observed and the adjusted means divided by the observed SD. An effect size of 0.8 SD should be considered as large, of 0.5 SD as medium and an effect size of 0.2 SD as small (Cohen 1988). Also we performed a sensitivity analysis to check whether imputation with the average score on the test or a score in between the worst and the average (25^{th} percentile) would alter the correlation coefficients between the measures of depression and the neuropsychological test scores.

Chi-square analysis was used to compare categorical variables and the independent samples t-test to compare continuous variables. Pearson's correlation coefficients were computed to study the associations between symptom measures of depression and neuropsychological test scores. Tests of significance were two-tailed ($P<0.05$).

4.4 RESULTS

In table 1 the baseline characteristics of the participants are presented. In 21 patients (39%) a diagnosis of MDD could be made according to DSM-IV criteria. Depressed patients tended to be younger and to have had more years of education than non-depressed patients, although this did not reach significance. In table 2, mean scores on various neuropsychological tests are reported and the result of adjustment for missing values is shown. All neuropsychological tests could be applied to more than 50% of this study sample. All patients except five participated in at least two of these tests. Only the adjustment after imputation of the worst score for the missing values due to cognitive

and behavioral reasons is shown. Imputation of neither the average test score nor the 25th percentile score did alter the associations shown hereafter. The effect size of the adjustment procedure was not acceptable for the BNT, Constructional praxis and WLM and therefore these tests were left out of further analysis.

Associations between measures of depression and neuropsychological test scores are presented in table 3. There was a negative correlation between the number of motivational symptoms and the Verbal (semantic) Fluency Tests (animals and professions) scores. None of the neuropsychological test results were significantly related to the number of mood symptoms, neither did they correlate with the total number of depressive symptoms. No association was found between total MMSE score and any of the measures of depression.

Table 1: Patient characteristics

	All patients N = 54	*MDD N = 21*	*No MDD N = 33*	
Age (mean)	73.7 (7.7)	71.5 (9.7)	75.2 (5.8)	P=0.087
Years of education (mean)	7.2 (3.1)	8.1 (3.4)	6.7 (2.8)	P=0.086
Female sex	25 (46)	9 (43)	16 (48)	n.s.
MMSE (mean)	19.8 (5.1)	20.3 (4.9)	19.6 (5.4)	n.s.
Previous stroke	17 (32)	4 (19)	13 (32)	n.s.
number of mood symptoms	0.70 (0.9)	1.52 (0.8)	0.18 (0.5)	$p < 0.001$
number of motivation symptoms	2.13 (1.3)	3.33 (0.7)	1.36 (1.0)	$p < 0.001$
total number of depressive symptoms	2.83 (2.0)	4.86 (1.2)	1.55 (1.0)	$p < 0.001$

MDD = Major Depressive Disorder; MMSE = MiniMentalStateExamination
numbers in brackets indicate SD (means) or percentage (prevalence)
P-value result from chi-square testing (percentages) or t-test (compare means)

Table 2: Observed and adjusted test-results: N =54, post stroke dementia

Tests:	Missing values	Observed mean (SD)	(still) missing values	Adjusted mean (SD)	Effect size (d)
Boston Naming Test	21	11.6(2.2)	3	9.9(2.8)	-0.8
Constructional Praxis	22	7.1(2.1)	3	4.8(3.4)	-1.1
Word list memory	21	12.6(3.5)	3	10.2(4.2)	-0.7
Word list recall	21	3.2(2.1)	7	2.3(2.3)	-0.4
Fluency animals	5	9.8(4.2)	0	9.0(4.7)	-0.2
Fluency professions	7	7.3(3.3)	0	6.4(4.0)	-0.3
Fluency letter B	11	5.3(3.4)	0	4.4(3.5)	-0.3

Table 3: Correlations between measures of depression and adjusted frontal test results: N = 54 (post stroke dementia)

	All depressive symptoms	Mood symptoms	Motivational symptoms
MMSE	-0.09[-0.35;0.18]	-0.03[-0.30;0.24]	-0.11[-0.37;0.16]
Word List Recall	-0.13[-0.38;0.14]	-0.11[-0.37;0.16]	-0.12[-0.38;0.15]
Fluency animals	-0.25[-0.49;0.02]	-0.14[-0.39;0.13]	-0.28[-0.51;-0.01] *
Fluency professions	-0.24[-0.48;0.03]	-0.10[-0.36;0.17]	-0.30[-0.53;-0.04] *
Fluency letter B	-0.15[-0.40;0.12]	0.01[-0.34;0.35]	-0.23[-0.47;0.04]

* $p < 0.05$, (two-tailed Pearson)
[Confidence Intervals in brackets]

4.5 DISCUSSION

The primary aim of the present study was to investigate the relationship between motivational symptoms of depression and fronto-subcortical dysfunction in 54 patients with post stroke dementia. The results on verbal semantic fluency tasks were negatively correlated with the number of motivational symptoms, indeed indicating a correlation between frontal dysfunction and motivational symptoms of the depressive disorder. Furthermore, we found that symptoms indicating motivation disturbance were highly prevalent in this group of patients with predominantly vascular dementia, in contrast to the symptoms of mood disturbance. Of the total number of depressive symptoms, 75% contributed to the factor motivation disturbance in the complete study sample. In 39% of the total sample, these symptoms occurred in the context of a major depressive episode. In these, the motivation symptoms contributed for as much as 68% to the total number of depressive symptoms. This is the same finding as we had in another group of demented subjects, although in that case, the level of dementia as well as that of depression was considerably less severe than in the present study (Janzing et al. 2005/chapter 5 this thesis). No significant relationships were observed between the mood symptoms and scores on neuropsychological tests and also consistent with earlier studies there was no significant correlation between a general measure of depression and specific neuropsychological tests performance (Kuzis et al. 1999). As was advocated by Smeding and De Koning (2000) we included missing values due to behavioural and/or cognitive disturbances. The effect size of this inclusion was medium or large for a large proportion of the tests used, but relatively small for the Verbal Fluency Test. The VFT is generally considered as a test of executive functioning (Lezak 1995). It is a measure of time-restricted generation of multiple-response alternatives under a constrained search condition. Important aspects of task performance are initiation, self-monitoring, retrieval and planning of goal

directed behaviour. In our study group the VFT seems therefore a reliable and useful test to measure frontal dysfunction in even severely demented patients.

The results of the present study should be interpreted in the context of the following limitations. First, a type 1 error can be expected when applying more than ten statistical tests on such a small study group. However, the result we found was in line with our hypothesis. Second, although the results refer to a clinical sample of subjects with post stroke dementia, some of them at least appeared to have a mixed type dementia (Vascular Dementia + AD). Moreover, we excluded patients with severe aphasia, thereby excluding patients with a specific cortical location which could be a possible bias in our study. Finally, replacing of missing values (imputation) is a valid statistical method for handling missing values, but remains a rather weak problem-solving approach. The sensitivity analysis which we performed showed that the results were not influenced by the height of the value which we chose for replacement. Moreover, the results still remained the same, even when we chose no imputation at all. Unfortunately, no specific neuropsychological (frontal) test is applicable to all patients in such a severely ill study-group. On the contrary, most of them were not useful in this study-group. Nevertheless, newer test should be developed, enabling the adequate measurement of frontal functioning in this category of patients.

Strengths of this study are that it is among the first to compare the effects of a broad range of depression parameters on cognitive deterioration in post stroke dementia and that it includes both categorical and dimensional measures of depression. Hence, detailed information on depressive symptoms was available, as well as test performance on different cognitive tests. Moreover, the group was thoroughly selected and revealed a rather large cohort of clearly defined clinical subjects.

This is the second study in which we have confirmed a relationship between low scores on the VFT and the motivational dimension of depression (Janzing et al. 2005 / chapter 5 this thesis). In contrast to our former study, there was no association between the MMSE total score and both the total number of depressive symptoms and the number of motivational symptoms.

Although the correlation between the verbal semantic fluency and motivational symptoms reached statistical significance, the actual correlation coefficients were weak: -.28(Confidence interval (CI) -0.51;-0.01) for VFT animals and -0.30(CI -0.53;-0.04) for VFT professions. In terms of clinical relevance this means that around 10% (square number of correlation coefficient) (CI 0.1%; 25%) of the variance in motivational symptoms can be explained by frontal dysfunction. That leaves open the question which other factors would clarify the other 90% of the variance of motivational symptoms.

There are no other reports of studies on this subject in patients with a diagnosis of post stroke dementia, but the findings in the present study are very similar to those of

Alexopoulos et al. who studied subjects with late-onset depression of presumed vascular origin (Kalayam & Alexopoulos 1999; Alexopoulos et al. 2000). In their studies executive dysfunction was found to be associated with poor or delayed antidepressant response in depressed elderly patients, with relapse and recurrence of geriatric major depression and with residual depressive symptoms. Unfortunately, they did not specify these residual symptoms in their study-groups. Our findings are also in line with the hypothesis that some features of the depressive disorder are an integral part of the degenerative process or illness. This is found in normal aging, senile dementia syndromes, or patients with subcortical brain diseases such as Huntington's and Parkinson's disease (Thompson et al. 2002; Leentjens et al. 2003). It is also in agreement with the "depression-executive dysfunction syndrome", which was proposed by Alexopoulos (2002) and comes very near to the concept of apathy, proposed by Marin (1990). Starkstein (2001) showed that the apathy syndrome occurred frequently in Alzheimer patients and in a majority of these the apathy syndrome co-occurred with a depressive disorder. Demarcation and clinical validation of these specific subsyndromes (i.e. apathy, low-motivational syndrome etc.) are still subject to debate and there may be no major difference between the motivation concept we used in this study, and the apathy concept postulated by others. For instance Kuzis (1999) showed that subjects with AD with a diagnosis of apathy (with or without depression) performed worse on the VFT and the Wisconsin Card Sorting Test. Scores on tests for memory, naming and block design were unrelated to apathy. Also McPherson (2002) found evidence for a specific relationship between apathy and neuropsychological tests measuring executive dysfunction in patients with AD. Using executive measures these authors were able to classify patients as apathetic or non-apathetic with 75% accuracy. Sperry (2001) reported significant correlation between apathy and naming and word list learning but the strongest relationship was with the VFT. A final study found that apathy scores of AD patients were predicted by verbal fluency scores but not by other neuropsychological tests (Paulsen et al. 1996). Lind (2002) performed a study on the relationship between regional brain symptoms and depressive symptomatology. Only five symptoms of the Comprehensive Psychopathological Rating Scale (CPRS) were assessed: depressed mood, anxiety, suicidal, hypochondriac and paranoid thoughts, but unfortunately not the motivational symptoms of depression. They nevertheless found that demented patients with a clinically established subcortical syndrome appeared to be more susceptible to depressive symptoms, which was not the case in patients with a prominent frontal syndrome. Lesser (1996) studied depressive features and cognitive function in patients with an early or late onset depression and healthy controls. They concluded that large amounts of white matter hyperintensities are more frequent in patients with late-onset depression than in elderly subjects with early-onset or no depression, and also that these patients show deterioration in information processing speed and have sig-

nificantly poorer executive function. These white matter hyperintensities are presumable of vascular origin and are often predominantly located in (frontal)-subcortical regions.

4.6 CONCLUSION

Fronto-subcortical dysfunction is partially responsible for the motivational but not the mood symptoms of depressive disorder in a group of patients with post-stroke dementia. Future studies should elucidate which other factors are related to the dimensions of depressive disorder in these patients and whether these findings have implications for therapeutic interventions.

Chapter 5

Depressive symptom quality and neuropsychological performance in dementia

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5.1 SUMMARY OF CHAPTER 5

It is unknown to what extent depression and cognitive dysfunction are related in subjects with dementia. A limitation of earlier studies is that only general measures of depression have been studied. In a sample of 60 subjects with dementia according to DSM-III-R criteria depressive symptoms were divided into factors of mood and motivation disturbance according to a principal components analysis. Correlations were computed between the factor scores and the performance on a number of specific neuropsychological tests. As the symptom content of motivation disturbance suggests subcorticofrontal dysfunction it was hypothesized that this factor is related to impaired executive functions.

Seventy-seven percent of the depressive symptoms contributed to the dimension of motivation disturbance and most of these symptoms occurred outside the context of a major depressive episode. Our hypothesis was supported by a significant negative correlation between motivation symptoms and semantic verbal fluency. This relationship seems to have specificity, as both the dimensions of mood symptoms and of general depressive symptoms did not correlate significantly with specific neuropsychological test scores.

The division of depressive symptoms in factors of mood and motivation disturbance contributes to insight into the relationship between depression and cognitive dysfunction in dementia. An advantage of the motivation disturbance factor compared to the regular apathy scales is that it consists of depressive symptoms. Therefore it becomes evident that apathy or impaired motivation may occur in patients with dementia both in and outside the context of a depressive syndrome.

5.2 INTRODUCTION

Depression frequently complicates the clinical course of dementia. Syndromal and subsyndromal depression has been reported in up to 50% of the patients that suffer from dementia (Ballard et al.1996; Lyketsos et al.1997; Janzing et al. 2002). A key question concerns the relationship between depression and cognitive dysfunction in dementia.

Studies considering the association between depression and general cognitive function have reported equivocal results. Increased prevalence of major depression was found in patients with lower (Rovner et al.1989), higher (Pearson et al.1989) and comparable (Kuzis et al. 1999) scores on the Mini Mental State.

The results of studies that have focused on the associations between depression and more specific cognitive deficits have also been inconclusive. Kuzis et al. (1999) reported that depressed and non-depressed patients with dementia were comparable in memory and executive functions. It has also been observed that patients with Alzheimer's Disease (AD) with and without depression had similar scores on tests of verbal and spatial performance (Berger et al. 2002). As subgroups were rather small, false negative results cannot be excluded in this study. In another study AD patients with depression performed more poorly on Block design, Digit Symbol and speeded motor programming, but performed better on a test of logical memory than non-depressed AD-patients (Wefel et al. 1999).

In these studies depression was defined according to general measures: depressive syndrome diagnoses according to the DSM classification system or scores on commonly used depression rating scales. An alternative approach is to study associations with qualitative measures of depressive symptoms. Recently, factors of mood and motivation disturbance have been demonstrated in depressive symptoms of demented subjects. Indeed, these factors had distinct associations with clinical characteristics of dementia (Forsell et al. 1993; Janzing et al.1999a).

The present study investigates the relationship between factors of mood and motivation disturbance and performance on a number of specific neuropsychological tests. It is hypothesized that the factor of motivation disturbance is most strongly related to cognitive dysfunction. As this factor seems to reflect subcortico/frontal pathology (Landes et al. 2001) it is expected that it particularly relates to impairment of executive functions.

5.3 METHODS

5.3.1 Subjects

Residents of six homes for the elderly in the region of Nijmegen, the Netherlands participated in this study. Informed consent was obtained from the subjects themselves or, in case of severe cognitive impairment, from close relatives.

In an earlier phase of the study 201 subjects were selected from a total population of 601 residents: 91 subjects with and 110 subjects without dementia. Subjects with dementia showed evidence of cognitive impairment according to two screening tests: a Mini Mental State Examination (MMSE) score ≤24 and Short Blessed Test (SBT) score >6 (Folstein et al. 1975; Katzman et al. 1983). In addition, they fulfilled the DSM-III-R criteria for dementia (APA 1987) based on information gathered with the Clinical Assessment Battery (CAB) of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Morris et al.1989). The type of dementia was not specified. Collateral information was obtained from both staff members of the homes and relatives of the subjects. Subjects without dementia had a normal cognitive function according to the screening instruments.

From the total population 194 residents refused to participate, 33 were unavailable (11 moved, 17 died, 5 too ill). From the remaining subjects, 76 did not fulfil the selection criteria and 97 were excluded (12 untestable, 37 CVA with normal cognitive function at screening, 7 Parkinson's Disease, 3 choreatic disease, 9 alcoholism, 10 partners of participants and 16 due to missing values of depressive symptoms).

The present study concerns only the subgroup of residents with dementia. From the 91 subjects originally selected, 17 refused neuropsychological testing and 14 had incomplete neuropsychological assessments. These subjects did not differ significantly from those with complete assessments with respect to demographic, cognitive and depressive characteristics. So the final sample consists of 60 subjects.

5.3.2 Measures of depression

All subjects underwent a full psychiatric assessment using the Geriatric Mental State (GMS community version) (Copeland et al. 1976).

Factors of mood and motivation disturbance were derived from a principal component analysis with varimax rotation on the criteria of DSM-III-R of major depressive episode of the original sample of 91 subjects with and 110 subjects without dementia (Janzing et al. 1999a). These factors were identical to those found in a larger population based study (Forsell et al. 1993).

For each subject in the present study three sum scores were computed by counting the positively rated contributing criteria:

(a) Depressive symptoms (sum score of all nine criteria of DSM-III-R major depressive episode).
(b) Mood symptoms (sum score of dysphoria, appetite disturbance, feelings of guilt and thoughts of death).
(c) Motivation symptoms (sum score of loss of interest, psychomotor change, loss of energy and thinking or concentration disturbance)

5.3.3 Neuropsychological assessment

Trained psychologists and medical or psychology students who had shown good inter-rater reliability administered the Neuropsychological Assessment Battery (NAB) of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al. 1989). Assessment was independent from the clinical interview and blinded for its results.

The following tests are included in the NAB:

1. Verbal Fluency; Animal Category (Isaacs et al. 1973). This test measures impairment in verbal production, semantic memory and language. Subjects are asked to name as many animals as possible in 60 seconds. The score is the total number of different animals named.
2. Modified Boston Naming Test (Kaplan et al.1978). Subjects are asked to name 15 objects presented as line drawings. A maximum of 10 seconds is allowed for each picture.
3. Word List Memory (Atkinson et al.1971). This task assesses the ability to remember newly learned information. It consists of 10 printed words presented in three trials in a random order. After each trial the subject is asked to recall as many items as possible. The maximum score is 30 for the three trials.
4. Constructional Praxis (Rosen et al.1984). In this task four line drawings are presented to the subject for copying in an increasing complexity (a circle, a diamond, intersecting rectangle and a cube). Two minutes are allowed for each figure.
5. Word List Recall. Delayed recall is tested for the 10 words presented in the Word List Memory Task. A maximum of 90 seconds is allowed.
6. Word List Recognition (Mohs et al.1986). Recognition is tested for the 10 words of the Word List Memory Task by presenting them among 10 distracter words. To adjust for chance, the total score is the sum of the number of correct answers minus 10.

5.4 STATISTICAL ANALYSIS

Pearson's correlation coefficients were computed to study the associations between symptom measures of depression and neuropsychological test scores. Tests of significance were two-tailed ($P<0.05$).

5.5 RESULTS

Sixty subjects were finally included in the present study. GMS-AGECAT (Copeland et al. 1988) diagnosed 55 of them as organic cases (18 level O3, 35 level O4 and 2 level O5). From the remaining subjects 2 were organic sub-cases and 3 had no diagnosis at the organic cluster according to GMS-AGECAT.

The subjects had a mean age of 86.3 (SD 5.6) years. Fifty-three subjects (88.3%) were female. Only 2 (3.3%) were married. On average the subjects had completed 7.2 (SD 2.2) years of education.

Table 1 presents the total number of depressive symptoms and the numbers of mood and motivation symptoms. The prevalence of depressive symptoms in the study sample is rather low. Regarding the nature of the symptoms, it can be concluded that they largely consist of motivation-based symptoms (1.0/1.3=77%). It should be noted that the maximum number of both mood and motivation symptoms is four.

Table 2 shows the neuropsychological test scores. The scores are comparable to those reported for AD patients with mild to moderate dementia (Morris et al. 1989). Regarding the distribution of the scores a floor effect seems to be present only in the scores for recall.

The results regarding the associations between measures of depression and scores on neuropsychological test are presented in table 3. A significant negative correlation between the number of motivation symptoms and the Verbal Fluency Test (VFT) scores was found. There was no significant relationship between motivation disturbance and performance on the other neuropsychological tests. Also, the correlation between total number of depressive symptoms or mood symptoms and neuropsychological test scores was insignificant.

5.6 DISCUSSION

The main finding of this study is a negative correlation between numbers of motivation symptoms and Verbal Fluency Test performance. This indeed supports our hypothesis that these symptoms reflect subcorticofrontal dysfunction. Furthermore, we found that

Table 1: Demographic and diagnostic characteristics of 60 subjects with dementia

	Mean (SD)
Age (years)	86.3 (5.6)
Sex (M/F)	7/53
Marital status	2 married / 58 unmarried
Education (years)	7.2 (2.2)
Depressive symptoms (number)	1.3 (1.5)
Mood symptoms (number)	0.3 (0.7)
Motivation symptoms (number)	1.0 (1.2)

Table 2: Test scores on neuropsychological tests of the NAB of 60 subjects with dementia

Neuropsychological test	**Mean (SD)**
Verbal Fluency	7.1 (4.1)
Boston Naming Test	8.5 (2.7)
Constructional Praxis	6.1 (2.6)
Word List Memory	8.2 (3.8)
Word List Recall	0.9 (1.2)
Word List Recognition	4.0 (3.0)
MMSE	16.6 (5.1)

Table 3: Correlations between measures of depression and neuropsychological test scores of 60 subjects with dementia

	VFT	**BNT**	**WLM**	**CP**	**Recall**	**Recognition**	**MMSE**
Depressive symptoms	-0.23	-0.08	-0.18	-0.21	0.09	0.00	-0.26*
Mood symptoms	-0.05	0.09	-0.06	-0.17	-0.05	0.02	-0.02
Motivation symptoms	-0.26*	-0.15	-0.20	-0.17	0.14	-0.02	-0.35**

VFT = Verbal Fluency; BNT = Boston Naming Test; WLM = Word List Memory; CP = Constructional Praxis; MMSE = Mini Mental State
*P<0.05; **P<0.01

symptoms indicating motivation disturbance were highly prevalent in patients with dementia, in contrast to the symptoms of mood disturbance. No significant relationships were observed between numbers of mood symptoms and scores on neuropsychological tests. Consistent with earlier studies there was no significant correlation between a general measure of depression and specific neuropsychological tests performance (Kuzis et al. 1999; Berger et al. 2002).

A strong point of our study is that we took a radically different approach in considering the nature of depressive symptomatology instead of classical depressive syndromes or scores on symptom scales. Forsell et al. (1993) originally reported the division of depres-

sive symptoms into mood and motivation disturbance factors in subjects with dementia. These factors have been replicated in a sample including the subjects of the present study (Janzing et al. 1999a). Subsequently, comparable dimensions have been demonstrated using different depression criteria (Janzing et al.1999b) and also in subjects with accurately diagnosed vascular dementia. (Naarding et al. 2003).

For both factors specific associations have been demonstrated with clinical characteristics of dementia. Mood symptoms predicted mortality rates of patients with mild dementia (Janzing et al.1999b). Motivation symptoms increased with the severity of dementia (Forsell et al. 1993; Janzing et al.1999a).

Considering the content of the motivation disturbance factor more carefully, it appears that it represents the core aspects of the syndrome of apathy. Indeed, Marin (1996) has shown that depressive symptoms like lack of interest, psychomotor retardation, lack of energy and lack of insight may be valid measures of apathy.

In the present study motivation symptoms predominated mood symptoms. From the total number of depressive symptoms 77% contributed to the factor motivation disturbance. Only in two subjects these symptoms occurred in the context of a major depressive episode.

As motivation disturbance is supposed to be the result of subcorticofrontal dysfunction it was hypothesized that it relates most specifically with neuropsychological tests measuring executive function. The association between motivation disturbance and impaired semantic verbal fluency is in support of this hypothesis. The VFT is generally considered as a test of executive functioning (Lezak 1995). It is a measure of time-restricted generation of multiple-response alternatives under a constrained search condition. Important aspects of task performance are initiation, self-monitoring, retrieval and planning of goal directed behaviour.

Observations of specific associations between apathy and executive dysfunction in dementia are in agreement with our findings. For instance Kuzis et al. (1999) showed that subjects with AD with a diagnosis of apathy (with or without depression) performed worse on the VFT and the Wisconsin Card Sorting Test. Scores on tests for memory, naming and block design were unrelated to apathy. Also McPherson et al. (2002) found evidence for a specific relationship between apathy and neuropsychological tests measuring executive dysfunction in patients with AD. Using executive measures these authors were able to classify patients as apathetic or non-apathetic with 75% accuracy. Sperry et al. (2001) reported significant correlation between apathy and naming and word list learning but the strongest relationship was with the VFT. A final study found that apathy scores of AD patients were predicted by verbal fluency scores but not by other neuropsychological tests (Paulsen et al. 1996).

Levels of mood symptoms were unrelated to scores on specific neuropsychological tests. However, it must be noticed that the variation in mood symptoms was rather low.

Associations between mood symptoms and specific neuropsychological tests have not been reported before. Although important differences exist, the dysphoria subscale of the Neuropsychiatric Inventory (NPI, Cummings et al. 1994) approaches the content of mood symptoms most closely. In agreement with Forsell's two-factor model it does not contain apathy related items. The dysphoria subscale contains questions regarding sadness, depressed mood, tearfulness, feelings of failure, hopelessness, guilt, and suicidal ideation. Using the NPI, McPherson et al. (2002) did not observe specific associations between dysphoria and executive dysfunction in patients with AD. From the other neuropsychological tests only block design correlated significantly with dysphoria.

We conclude that the two-factor model of depressive symptoms contributes to our insight into the relationship between depression and cognitive dysfunction in dementia. Only after the division of the criteria of major depressive disorder into qualitatively different factors, an association between motivation disturbance and executive dysfunction became observable that seems to be replicable across studies.

In contrast to measures of apathy like the Apathy Evaluation Scale (Marin et al. 1991) or the apathy subscale of the NPI the factor motivation disturbance consists of depressive symptoms. Therefore it is easy to understand that apathy is not just a syndrome associated or coexistent with depression, as is suggested by the 'external' scales, but may represent the core part of a depressive syndrome itself. It is therefore evident that symptoms of apathy or impaired motivation may occur in patients with dementia both in and outside the context of a depressive syndrome.

There are a number of limitations to the present study. First the study took place in residents of homes for the elderly. Although the two-factor model has proved to be applicable in different populations, it is unclear to what extent the observed correlation between the factors and the neuropsychological performance can be generalized. Second, although significant, the correlation between motivation disturbance and verbal fluency was only moderate. As this correlation confirmed our specific hypothesis and is in accordance with studies using apathy rating scales we concluded that reporting it was relevant. Furthermore, in a different sample consisting of patients with vascular dementia we found a correlation of comparable size between motivation symptoms and the VFT (Naarding et al. submitted, chapter 4 of this thesis). The presence of a floor effect may have obscured possible relationships between the measure of recall and the factors of depressive symptoms. Finally, only one measure of executive function was available in the CERAD neuropsychological battery. It is clear that to substantiate the findings of the present study the assessment of a broader set of tests for executive functions will be essential.

Chapter 6

A study on symptom profiles of late-life depression: the influence of vascular, degenerative and inflammatory risk-indicators

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6.1 SUMMARY OF CHAPTER 6

If specific symptom profiles of depressive disorders in the elderly are related to a specific aetiology, this could have implications for everyday clinical practice. We hypothesized that a 'motivational' profile, with symptoms such as psychomotor change, loss of interest and loss of energy could clinically separate patients with predominantly vascular or degenerative risk from patients with an inflammatory risk. A total of 4051 subjects participated in a study on mental health problems in community dwelling elderly. Information on psychiatric symptoms, demographic and medical status, previous history and family history was obtained. We distinguished three subgroups according to the predominant somatic risk-indicators; a vascular, degenerative and inflammatory group. Motivational symptoms were associated with vascular or degenerative risk-indicators for depression; psychomotor change with both indicators, loss of energy specifically with the vascular, and thinking/concentration disturbance with the degenerative indicator. The so-called mood symptoms of depression, especially thoughts of death, were more strongly associated with the inflammatory risk-indicator. Melancholic symptoms like appetite and sleep disturbances were more strongly associated with the inflammatory risk-indicator. Although etiological classification was not confirmed by additional investigations such as laboratory findings or MRI brain scans, this study showed that in patients with a late-life depression specific symptoms of the depressive disorder may reflect the predominant underlying pathogenic mechanism.

6.2 INTRODUCTION

Depressive disorders are among the major causes of disability worldwide (WHO 2001). Especially in the elderly, depressive disorders are found in a large number of patients who also suffer from other diseases, such as chronic heart disease, stroke or dementia. While these diseases increase the risk of developing depression, depression also substantially contributes to morbidity and mortality in patients with somatic disease (Penninx et al. 1998;Penninx et al. 1999;Schoevers et al. 2000b). For depressive disorders in the elderly, especially those with a late-onset of the depression, three predominant etiological paradigms can be used. The 'degenerative' paradigm is probably the oldest; it regards depression in the elderly as a precursor of subsequent cognitive decline and eventually dementia (Emery & Oxman 1992). The second is the 'vascular depression' hypothesis that was revitalized some years ago (Alexopoulos et al. 1997). Vascular lesions in the brain have long been known to be associated with higher incidence rates for depressive disorder, and neuroimaging often shows small, 'silent' cerebral infarcts and white matter lesions in patients with a late-onset depressive disorder (Fujikawa et al. 1993). Finally, the 'inflammatory' paradigm was introduced, based on the discovery of elevated levels of inflammatory markers in (elderly) patients with a depressive disorder (Penninx et al. 2003). Furthermore, in patients with (auto) inflammatory diseases like rheumatoid arthritis, an increased incidence of depressive disorder is found.

It has been suggested that the nature of depressive symptoms varies with the presumed pathogenesis of the depressive disorder. Forsell demonstrated subgroups of depression in the elderly, characterized by a 'low motivation' or a 'low mood' syndrome. An "organic" syndrome was more often found in patients with predominantly 'motivational' than in those with predominantly 'mood' symptoms (Forsell et al. 1993). Others confirmed this finding (Janzing et al. 1999a) and recently we have shown that these symptom profiles indeed indicate the extent of vascular damage in a group of patients with post-stroke depression (Naarding et al. 2003). The "mood" profile is made up of symptoms such as dysphoria, anger, negative and suicidal thoughts, ruminations and social withdrawal. The "motivation" profile includes psychomotor retardation, a sad appearance, thinking/concentration disturbances, loss of interest and loss of energy. In the present study we set out to explore whether the symptom profile of depression in a large representative sample of community-dwelling elderly reflects the underlying pathogenic mechanisms of depression. Each subject was scored positive or negative on three risk-indicators, 'degenerative', 'inflammatory' or 'vascular'. The presence of depressive symptoms and syndromes was then established for each group. The primary aim of this study was to assess whether specific symptom profiles of the depressive disorder are associated with one of the specific risk-indicators. Our hypothesis was that a 'motivational' symptom profile could clinically separate the vascular and degenerative from the inflammatory group.

6.3 METHODS

6.3.1 Subjects

The Amsterdam Study of the Elderly (AMSTEL) is a prospective study of a large, representative sample of community dwelling elderly that assesses mental health problems, medical diagnoses and demographic characteristics. The sampling and data collection procedures have been described elsewhere (Launer et al. 1993; Schoevers et al. 2000a). In short, the population base for AMSTEL included all non-institutional individuals in the 65-84 age brackets who lived in the city of Amsterdam. The profile of the study sample corresponded to the non-institutionalized Amsterdam population in terms of age and gender. An age-stratified sample was drawn. All 4051 subjects (71.5%) who responded and gave their informed consent were interviewed at baseline. Non-response in the younger old (<75) was associated with poor performance on cognitive tests and with health problems. In the older old no correlates of non-response were found (Launer et al. 1994).

The subjects were interviewed to gather information on psychiatric symptoms, demographic and medical status, previous history and family history. The interview was based on the Dutch translation of the Mini-Mental State Examination (MMSE) (Folstein et al. 1975), all Geriatric Mental State (GMS) Examination-items related to organic, affective and anxiety syndromes (Copeland et al. 1986), the Activities of Daily Living (ADL) scale (Katz et al. 1963), the Instrumental Activities of Daily Living (IADL) scale (Lawton & Brody 1969), and the CAMDEX-interview (Roth et al. 1986). The interview was administered during home visits by lay interviewers who were specially trained using video sessions and were regularly supervised.

6.3.2 Psychiatric evaluation

Diagnoses of dementia and depression were made according to the GMS-AGECAT system (Copeland et al. 1986; Copeland et al. 1988). The Dutch language version has proven reliability for epidemiological work in replication studies (Hooijer et al. 1991). Apart from the GMS-AGECAT diagnosis of dementia, cognitive status was also assessed by the MMSE-score (Folstein et al. 1975). Depression case-ness was defined as a GMS-AGECAT level 3 or higher. A distinction is made between neurotic and psychotic depression, indicating increasing severity levels of depression. As this subdivision of depression is partly based on etiological notions and does not completely overlap with the DSM-categories of major and minor depression (APA 1987; 1994; Lobo et al. 1995) a separate classification of depression was also made that reflects these DSM criteria. If subjects had either 'depressed mood' or 'loss of interest or pleasure', and a total of 5 or more of the nine DSM-III-R depression symptoms, they were classified as major depression. Subjects who had either 'depressed mood' or 'loss of interest or pleasure' and a total of at least two but

no more than four depression symptoms were classified as minor depression. According to the profiles found by Forsell and Janzing, for each individual the following measures of depression were computed by counting the positively rated criteria (Forsell et al. 1993; Janzing et al. 1999a).

- Mood symptoms (dysphoria, appetite disturbance, feelings of guilt and thoughts of death).
- Motivational symptoms (loss of interest, psychomotor change, loss of energy and thinking or concentration disturbance)

6.3.3 Pathogenic risk-indicators

The presence of chronic diseases was assessed with the pertinent Camdex questions on cardiovascular diseases, cancer, lung disease, diabetes, Parkinson's disease, arthritis and epilepsy. Patients were assigned to a subgroup according to the presence of one of the three etiological risk-indicators. The vascular group contained patients who had suffered a stroke or myocardial infarction. The degenerative group comprised patients who according to the GMS were "organic" cases, i.e. that the score on this item was 3 or higher (GMS-AGECAT)(Copeland et al. 1986). Finally, the inflammatory group consisted of patients with chronic rheumatic disease or arthritis.

6.4 STATISTICAL ANALYSIS

For statistical analysis we used the Statistical Package for the Social Sciences (SPSS) for Windows version 12.0. Chi-square analysis was used to compare categorical variables and the independent samples t-test to compare continuous variables. Prevalence of major and minor depression was established for the three risk-groups. Prevalence and odds ratio of specific depressive symptoms were calculated for the three risk-groups. Multinomial regression analysis was used to find out whether specific depressive symptoms or a mood/motivation subsyndrome would predict specific risk-indicators, controlling for potential confounders. A backward stepwise analysis was used to reach the most parsimonious model for each risk-indicator.

When the 95% confidence interval of the odds ratio did not include 1, the association was regarded to be statistically significant. Differences between strata were considered statistically significant according to the criterion that the confidence intervals of a risk-indicator mutually exclude the point estimates in one or both of the other diagnostic categories (Gardner & Altman 1986).

6.5 RESULTS

6.5.1 General characteristics of the study group

Of the total of 4051 subjects, 607(15%) could be classified as 'vascular', 694(17%) as 'inflammatory' and 261(6%) as 'degenerative' cases. There was some overlap between these categories, as there were subjects who met the criteria for more than one etiological category. After excluding these subjects, our study group consisted of 496 vascular, 171 degenerative and 583 inflammatory cases. Table 1 shows the general characteristics of the original study group and the risk-indicator groups. There were some statistically significant differences between the three groups as compared to the total study group. Subjects with a vascular risk-indicator were more often male (chi-square = 63.497, df 1, $p < 0.001$), subjects with a degenerative risk-indicator were older ($t = -7.591$, df 4049, $p < 0.001$), received less years of training ($t = 6.267$, df 4025, $p < 0.001$) and had lower MMSE scores ($t = 38.131$, df 4049, $p < 0.001$), and those with an inflammatory risk-indicator tended to be more often female (chi-square = 98.110, df 1, $p < 0.001$) and were more on antidepressant medication. (chi-square = 11.354, df 1, $p = .001$)

6.5.2 Prevalence of depressive syndromes and symptoms

Major as well as minor depressive disorders (MajDD and MinDD, respectively) were found in significant proportions in all three subgroups (table 2). In agreement with earlier studies, our results indicated that the odds of having a MajDD was about 2 – 3.5 times higher in subjects with one of the three specific risk-indicators compared to subjects with none of the risk-indicators. In the vascular group the odds ratio was 2.39 (95%CI 1.55 – 3.67), in the degenerative group 3.37 (95% CI 1.91 – 5.93) and in the inflammatory group 2.80 (95% CI 1.89 – 4.15). For MinDD no increased risk was found in the degenerative subgroup, while in the vascular subgroup the odds ratio was 1.63 (95% CI 1.25 – 2.13) and in the inflammatory subgroup 2.23 (95% CI 1.76 – 2.82). The confidence intervals of the vascular subgroup and that of the inflammatory group mutually excluded each others point estimate on behalf of the minor depression. The interpretation could be that the inflammatory group is stronger associated with this minor depressive disorder than the vascular group.

The results of the bi-variate analysis of individual depressive symptoms and their relation with the three risk-indicators are shown in Table 3. Virtually all symptoms of depression were more prevalent in the risk-groups than in the group without any risk, except for depressed mood and feelings of guilt in the vascular subgroup and sleep disturbance and feelings of guilt in the degenerative subgroup. According to the criterion of confidence intervals mutually excluding point estimates, the following symptoms showed significant statistical differences between different strata : loss of interest was associated more strongly with the degenerative risk than with the inflammatory risk; psychomotor

Table 1: General characteristics

	Total group	*No risk-indicator*	*Vascular*	*Degenerative*	*inflammatory*
Group size	4051	1797	496	171	583
Age	75.4 (5.7)	74.8 (5.7)	75.8 (5.5)	78.6 (5.5)*	76.0 (5.6)
Years of education	8.2 (2.5)	8.4 (2.5)	8.1 (2.4)	7.0 (1.9)*	8.0 (2.5)
Female sex (%)	62.4	61.9	46.2*	66.7	80.8*
Antidepressant use (%)	4.1	3.5	3.2	5.8	6.7*
MMSE	26.9 (3.8)	27.8 (2.1)	26.4 (4.4)	17.6 (8.1)*	26.9 (3.3)

MMSE = MiniMentalStateExamination
Numbers in brackets indicate SD (means)
In the risk-indicator groups only the 'pure' risk-indicator cases are included
* differ significantly (p at least smaller than 0.05) from total group based on t-test (means) and x^2-test (percentages) (see text)

change showed a stronger association with the degenerative than with both the vascular and inflammatory risk; thinking/concentration disturbance was most strongly-associated with the degenerative risk group, but also yielded a stronger association with the inflammatory than with the vascular risk group.

The parsimonious models (table 4) for each of the three risk-indicator groups consisted of a smaller number of the depressive symptoms that were not the same for each of the groups. The model fitted adequately to the data (Pearson's Goodness-of-fit chi-square 12400.58, df 12728, p = 0.981). The presence of a vascular risk-indicator was predicted by sleep disturbance, psychomotor change and loss of energy. The organic risk-indicator was predicted by psychomotor change and thinking/concentration disturbance and finally the inflammatory risk-indicator was predicted by loss of appetite, sleep disturbance, loss of energy, thinking/concentration disturbance and thoughts of death. Clustering of symptoms into a mood and motivation component according to Forsell (Forsell et al. 1993) did not improve the model. (data not shown)

Table 2: Prevalence of major and minor depressive disorder in LLD with a vascular, degenerative or inflammatory risk-indicator

	N =	***Maj DD***	***Odds ratio***	***Min DD***	***Odds ratio***
		N (%)		*N (%)*	
Total group	4051	217 (5.4)	–	660 (16.3)	–
No risk-indicator	1797	57 (3.2)	–	224 (12.5)	–
Vascular	496	36(7.3)	2.39 [1.55 – 3.67]	94(19.0)	1.63 [1.25 – 2.13]
Degenerative	171	17(9.9)	3.37 [1.91 – 5.93]	28(16.4)	1.37 [0.89 – 2.10]
Inflammatory	583	49(8.4)	2.80 [1.89 – 4.15]	141(24.2)	2.23 [1.76 – 2.82]

LLD = late-life depression; Maj DD = Major depressive disorder; Min DD = Minor depressive disorder
Odds ratios were calculated comparing one of the risk-groups to subjects with none of the risk-indicators
95% Confidence Intervals (CI) are shown in bracket

Table 3: DSM-IV depressive symptoms in subgroups with a vascular, degenerative or inflammatory risk-indicator

	Vascular		*Degenerative*		*Inflammatory*		*No risk indicator*	All Subjects
DSM-IV symptom	*%*	*Odds ratio*	*%*	*Odds ratio*	*%*	*Odds ratio*	*%*	*%*
I Depressed mood	9.9	1.36 [0.97 – 1.92]	14.0	2.03 [1.27 – 3.23]	15.4	2.27 [1.70 – 3.01]	7.5	9.9
II Loss of interest	13.9	2.24 [1.63 – 3.06]	17.0	2.83 [1.82 – 4.39]	11.1	1.74 [1.26 – 2.39]	6.7	9.2
III Appetite disturbance	7.5	2.22 [1.46 – 3.37]	9.9	3.04 [1.73 – 5.32]	9.1	2.75 [1.89 – 4.02]	3.5	6.0
IV Sleep disturbance	29.6	1.44 [1.16 – 1.80]	24.0	1.08 [0.75 – 1.56]	33.3	1.71 [1.39 – 2.10]	22.6	27.0
V Psychomotor change	12.3	2.57 [1.83 – 3.61]	21.1	4.89 [3.20 – 7.46]	9.9	2.02 [1.44 – 2.85]	5.2	8.7
VI Loss of energy	37.1	2.20 [1.77 – 2.73]	30.4	1.63 [1.15 – 2.30]	37.4	2.23 [1.82 – 2.73]	21.1	29.2
VII Feelings of guilt	2.2	0.60 [0.32 – 1.15]	1.8	0.48 [0.15 – 1.53]	6.0	1.70 [1.12 – 2.60]	3.6	3.6
VIII Thinking/concentration	23.8	1.35 [1.06 – 1.71]	43.3	3.29 [2.38 – 4.56]	30.0	1.85 [1.50 – 2.29]	18.8	23.5
IX Thoughts of death	13.5	1.91 [1.41 – 2.60]	14.6	2.09 [1.32 – 3.31]	16.1	2.35 [1.77 – 3.11]	7.6	10.9

Odds ratios are calculated comparing one of the risk-indicator groups to subjects with none of the risk-indicators
95% Confidence Intervals (CI) are shown in brackets

Table 4. Adjusted Odds ratios (ORs) of vascular, degenerative or inflammatory risk-indicators according to depressive symptom profile (N = 3047, most parsimonious models with p in < 0.05, p out > 0.10, backstep procedure)

Risk-indicator	*Vascular*	*Degenerative*	*inflammatory*
DSM-IV symptom			
Age	–	1.08 [1.04 – 1.12]	1.02 [1.00 – 1.04]
Sex	2.22 [1.82 – 2.78]	–	2.17 [1.72 – 2.75]
Education level	–	–	–
Antidepressant use	–	–	–
MMSE	1.18 [1.14 – 1.22]	1.45 [1.39 – 1.52]	0.89 [0.86 – 0.93]
Appetite disturbance	–	–	1.91 [1.28 – 2.83] §
Sleep disturbance	1.44 [1.13 – 1.83] §	–	1.29 [1.04 – 1.61] *
Psychomotor change	1.78 [1.22 – 2.60] §	2.06 [1.13 – 3.75] *	–
Loss of energy	1.83 [1.45 – 2.31] #	–	1.73 [1.39 – 2.14] #
Thinking/concentration	–	1.72 [1.12 – 2.65] *	1.26 [1.00 – 1.59] *
Thoughts of death	–	–	1.49 [1.10 – 2.03] *

Odds ratios are adjusted by age, sex, education-level, anti-depressant use and score on MiniMental State Examination (MMSE).
* p<.05; §p <.01; # p<.001

6.6 DISCUSSION

In this population-based study, we investigated whether in subjects with depression the clinical psychiatric profile was related to the risk-indicators for the depressive disorder. This study showed that indeed some of the motivational symptoms, i.e. psychomotor change and loss of energy were more strongly associated with the vascular and degenerative risk-indicator than with the inflammatory risk-indicator. Mood symptoms, especially thoughts of death and also melancholic symptoms like sleep and appetite disturbances were more strongly-related with inflammatory risk as opposed to both the degenerative and vascular risk.

Although depression comprises various symptoms that are traditionally grouped in different clusters, the concept of depression as a single syndrome that represents a final common pathway of a broad range of biological as well as psychological factors has become widely accepted over recent decades (Parker 2000). This 'single syndrome' concept is reflected in the current classification systems DSM-IV and ICD-10. Especially in subjects for whom a specific cause is presumed, specific clinical profiles may be detected, and therefore it has been suggested that old paradigms should be revived (Parker 2000). More accurate definitions of the subgroups and also more accurate demarcation of different depressive syndromes will become possible, with the advent of new neuroimaging and

laboratory investigations. Clustering of symptoms into specific symptom dimensions can increase the likelihood of a familial and possibly genetic etiology (Korszun et al. 2004).

In our previous studies we showed a relationship between a specific 'motivation' component and neurodegenerative or vascular damage of the brain (Janzing et al. 1999;Naarding et al. 2003). Others have mentioned an 'apathetic' sub-syndrome that was related with degenerative brain diseases (Marin 1996;Starkstein et al. 2001). It has been suggested that the 'mood' symptoms represent a more psychological reaction to the consequences of a chronic disease and that one would need a brain that works relatively well to develop these mood or cognitive symptoms. This has fostered the notion that these mood symptoms can be predominantly found in a subgroup of patients with comparable disability and suffering, but with intact brain function, represented by the inflammatory group in the current study. On the other hand, recent studies have shown that inflammation, vascular and cellular degeneration are all interrelated, and perhaps even share a common pathogenesis (Jerrard-Dunne et al. 2004;van den Biggelaar et al. 2004). Despite the fact that there is overlap between the various groups, our study showed that the distinct risk-indicators we used were associated with distinct symptom profiles of depression.

The clinical relevance of our findings is that when etiological risk-indicators can be linked to the clinical presentation of depressive disorder in the elderly, therapeutic as well as preventive strategies can be better adjusted to the specific needs of the individual subject. In case of a predominant 'motivational' profile, special attention should be paid to the presence of vascular risk and the probability of an imminent degenerative disease should be taken into account.

Our study has several limitations. Most importantly, etiological classification was not confirmed by additional investigations such as laboratory findings for the inflammatory group, or brain MRI for the vascular or degenerative group. We have previously found that the concordance between self-reported physical illness and the data supplied by the GP's was satisfactory and was not affected by levels of depression (Kriegsman et al. 1996). It is therefore very unlikely that misclassification of risk-indicator status has had a major influence on our results (Rothman & Greenland 1998). However, the findings need replication in a study with more elaborate measures of risk-indicators. A second limitation of our study is that the cross-sectional design of this study does not allow the ascertainment of causal and temporal relationships. However, as there is no reason to believe that lack of data on temporal relationships would differentially affect any of the three risk-indicators under study, the effect on the current results is probably limited. Finally, early stages of dementia may not be classified as organic cases in our study. It is well known that there is a great deal of crossover of symptoms of depression with mild cognitive impairment or subjective memory complaints. To our knowledge, not only the GMS-AGECAT diagnostic procedure is particularly sensitive to this problem, but it would be the case with other diagnostic instruments. Moreover, misclassification

of subjects would lead to leveling of differences and therefore it is unlikely that it has had a major influence on the final results.

One of the strengths of our study is that we studied a relatively large group of subjects, who were representative of the general population. Our subgroups with the three risk-indicators were large enough to analyze reliably, especially because the overlap between the three groups was quite modest. Furthermore, the diagnostic procedure for psychiatric and organic disorder was quite detailed and accurate.

In conclusion, our study suggests that in patients with late-life depression specific symptoms of the depressive disorder may be used as indicators of the predominant underlying pathogenic factor. If replicated, this may have important implications for our understanding of the nature of depression and the associations with different pathophysiological disease mechanisms. This may be important for the adjustment of therapeutic as well as preventive strategies for these patients.

Chapter 7

Clinically defined vascular depression in the general population

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7.1 SUMMARY OF CHAPTER 7

Vascular depression is regarded as a subtype of depression, especially in - but not strictly reserved to - the elderly, characterized by a specific clinical presentation and an association with (cerebro)vascular risk and disease. It could have major implications if subjects at risk for such a depression could easily be identified by their clinical presentation in general practice. We therefore studied the symptom profile of depression in subjects with and without vascular risk in two large community studies, the Rotterdam Study and the Amstel study, in the Netherlands. We used the original description of vascular depression by Alexopoulos. We could not confirm the specific symptom profile in depressed subjects with vascular risk factors in either of the two cohorts. In the Rotterdam Study, depressed subjects with vascular risk factors showed more loss of energy and more disability. Presumed specific symptoms of vascular depression, psychomotor changes and anhedonia, however, were not significantly associated with any of the vascular risk indicators. Loss of energy showed a significant association with myocardial infarction and peripheral arterial disease in this sample. In the Amstel study, a significant association between vascular risk factors and loss of energy and appetite disturbance was found in all subjects, either depressed or not.

7.2 INTRODUCTION

The vascular depression hypothesis states that especially in the elderly a subtype of depressive disorder exists that is caused by vascular brain disease. This hypothesis is a very old one. Around 1900, a German psychiatrist named Gaupp (1905) already mentioned 'atherosclerotic depression'. The concept was revitalized by Krishnan et al. (1997) and Alexopoulos et al. (1997a; 1997b) in the 1990s, boosted by the development of new imaging techniques. Krishnan coined this entity "MRI defined vascular depression", with the vascular lesions on MRI as the obligatory finding. Next to the vascular characteristics, this group of patients could be recognized by a specific symptom profile of the depression. According to Alexopoulos the characteristics of this vascular depression include more pronounced psychomotor change, greater overall cognitive impairment and disability, fewer feelings of guilt and greater lack of insight. The MRI-defined vascular depression group of Krishnan showed a similar picture; the subjects in his study were older, had a later age of depression-onset and showed more anhedonia and disability. Furthermore, he found that the non-psychotic symptoms prevailed whereas a family history of mental illness was less common. Both studies were conducted in hospital based settings which limits generalization to the general population. The clinical importance of recognizing vascular depression as a subtype of affective disorder would be enhanced if it were possible to identify patients by simple tests or procedures, such as through specific symptoms or risk-profiles. The recognition of such a specific subtype of depression could be of major importance in predicting the course of illness and the effect of medication and other therapeutic interventions. In the present study, we tried to assess these phenomenological characteristics of depressed subjects with and without vascular disease in the general population. If the vascular depression hypothesis is correct, subjects with a vascular risk would show more anhedonia and psychomotor change, and less feelings of guilt. Furthermore, we expected them to show more disability.

7.3 METHODS

7.3.1 Subjects and procedures

Subjects were recruited from two large samples of community dwelling elderly, The Amsterdam Study of the Elderly (AMSTEL) and the Rotterdam Study. The AMSTEL study is a prospective study that assesses mental health problems, medical diagnoses and demographic characteristics. The sampling and data collection procedures have been described elsewhere (Schoevers et al. 2000a). In short, the population base for AMSTEL included all non-institutional individuals in the 65-84 age brackets who lived in the city of Amsterdam. The profile of the study sample corresponded to the non-institutionalized

Amsterdam population in terms of age and gender. An age-stratified sample was drawn. All 4051 subjects (71.5%) who responded and gave their informed consent were interviewed at baseline. Non-response in the younger old (<75) was associated with poor performance on cognitive tests and with health problems. In the older aged no correlates of non-response were found (Launer et al. 1994).

The subjects were interviewed to gather information on psychiatric symptoms, demographic and medical status, previous history and family history. The interview was based on the Dutch translation of the Mini-Mental State Examination (MMSE) (Folstein et al. 1975), all Geriatric Mental State (GMS) Examination-items related to organic, affective and anxiety syndromes (Copeland et al. 1986), the Activities of Daily Living (ADL) scale (Katz et al. 1963), the Instrumental Activities of Daily Living (IADL) scale (Lawton & Brody 1969), and the CAMDEX-interview (Roth et al. 1986). The interview was administered during home visits by lay interviewers who were specially trained using video sessions and were regularly supervised.

The aim of the Rotterdam Study is to investigate determinants of chronic and disabling diseases. The study started in 1990, when all inhabitants 55 years old and above in Ommoord, a district of Rotterdam, the Netherlands, were invited to participate. Sampling procedure and response rate have also been described elsewhere (Hofman et al. 1991). In this paper, data of 4603 subjects is used from the second follow-up survey in 1997 to 1999. In this survey assessment of depressive symptoms was added to the study protocol. In addition, the total cohort is continuously being monitored for major morbidity and mortality through linkage of general practitioner and municipality records. Both studies were approved by the local Medical Ethics Committee and written informed consent was obtained from all participants.

7.3.2 Psychiatric evaluation

In the AMSTEL study, diagnoses of dementia and depression were made according to the GMS-AGECAT system (Copeland et al. 1986; Copeland et al. 1988). The Dutch language version has proven reliability for epidemiological work in replication studies (Hooijer et al. 1991). Apart from the GMS-AGECAT diagnosis of dementia, cognitive status was also assessed by the MMSE-score (Folstein et al. 1975). 'Depressive caseness' (i.e. depression warranting intervention as defined by psychiatrists) was defined as a GMS-AGECAT level 3 or higher.

In the Rotterdam Study diagnosis of depression was assessed by a two-step procedure. First, participants completed the Dutch version of the Center for Epidemiological Studies Depression Scale (CES-D) during the home interview. We used a score of 16 as a cut-off to indicate depressive symptoms. This cutoff had a very high sensitivity for major depression in another Dutch study in the elderly (Beekman et al. 1997b). In a second step, screen-positive subjects had a psychiatric workup. Of the 4603 subjects, 364 (7.9

%) were screened positive as measured by the CES-D and the psychiatric work-up was performed in 333 of the remaining participants. They were studied with the Dutch version of the Present State Examination, a semi-structured psychiatric interview included in the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO 1997). All interviews were conducted by one of two experienced clinicians. Depressive disorders were classified according to the DSM-IV (APA 1997) criteria with an algorithm based on the GMS-scores (AMSTEL) and SCAN scores (Rotterdam Study). If subjects had either 'depressed mood' or 'loss of interest or pleasure', and a total of 5 or more of the nine DSM-IV depression symptoms, they were classified as major depression. Subjects who had either 'depressed mood' or 'loss of interest or pleasure' and a total of at least two but no more than four depression symptoms were classified as minor depression. According to the profiles found by Forsell and Janzing, for each individual the following measures of depression were computed for both study groups (AMSTEL and ERGO) by counting the positively rated criteria (Forsell et al. 1993; Janzing et al. 1999a).

- Mood symptoms: Dysphoria, appetite disturbance, feelings of guilt and thoughts of death.
- Motivational symptoms: loss of interest, psychomotor change, loss of energy and thinking or concentration disturbance.

Finally, we dichotomized subjects according to the presence of some of the typical symptoms of "vascular depression" that were reported in the literature: anhedonia, psychomotor change and loss of energy.

7.3.3 Vascular risk

In the original study by Alexopoulos vascular risk was defined according to the score on the Cumulative Illness Rating Scale (CIRS) (Miller et al.1992). The original CIRS consists of multiple organ-specific categories, but for the vascular depression categorization only the vascular subscale was used by Alexopoulos. A score equal to or greater than 1 on the CIRS assigned the subject to the vascular group. We have classified our subjects from both the Amstel and the Rotterdam study on the same criteria yielding comparable 'vascular' and 'non-vascular' groups. Next, we have divided our sample in (1) a group of patients without any vascular risk factor, (2) a group of patients with only vascular risk factors, but no apparent vascular disease and (3) a group of patients with evident vascular disease. In the end, this more detailed subdivision had no influence on the results, so we have only used the original categorization following Alexopoulos.

In addition, in the Rotterdam Study, vascular risk was studied more extensively. Of the depressed subjects (N=333) who participated in the home interview, 246 came to the research centre for non-invasive assessments of atherosclerosis. The 87 subjects with no assessment of atherosclerosis were on average older (79 vs. 74 years) and had more depressive symptoms (total number of depressive symptoms 3.2 [SD 2.3] vs. 2.5 [SD 2.0],

overall total number 2.7 [SD 2.1]). There was no difference in gender between the participants and non-participants (78% female, vs. 74%).

We measured atherosclerosis non-invasively with 4 established methods, i.e. the ankle-brachial blood pressure index, intima-media thickness in the common carotid arteries, the presence of plaques in the carotid arteries and aortic atherosclerosis. These measures assess extra-coronary atherosclerosis at different locations in the body. All measures are strongly associated with incident cerebrovascular and coronary artery disease (Witteman et al. 1986; McKenna et al. 1991; Hollander et al. 2002). Details of these assessments are outlined in an earlier publication (Tiemeier et al. 2004).

7.3.4 Other measurements

In both studies confounders were assessed in very similar manners. Age, sex, education, cognitive function, cigarette smoking, blood pressure, diabetes mellitus, history of myocardial infarction and/or stroke, total cholesterol level, body mass index and use of antidepressant medication were all accounted for. Education was dichotomized into low (only primary school or less) or high education. Depression severity was measured only in the Rotterdam Study with the Hamilton Depression Rating Scale (HAMD) (Hamilton 1960). Cigarette smoking was coded into categories of current, former or never smoker. History of myocardial infarction or stroke was only considered positive when it was verified by a physician. Total cholesterol level was only assessed in the Rotterdam Study and was analyzed in fasting blood samples by an automatic enzymatic procedure. Body mass index was calculated using the Quetelet method (weight in kilograms divided by the square of height in meters) and was only done in the Rotterdam study. Information on antidepressant medication was obtained in the home-interviews and in the Rotterdam study it was secured by a cabinet check.

7.4 STATISTICAL ANALYSIS

For statistical analysis we used the Statistical Package for the Social Sciences (SPSS) for Windows version 12.0. Chi-square analysis was used to compare categorical variables and the independent samples t-test to compare continuous variables. Prevalence of major and minor depression was established for the vascular and the non-vascular group and also the mean total number of depressive symptoms as well as the specific mean number of mood and motivation symptoms were counted. The vascular depression hypothesis was tested first by replicating the method of Alexopoulos et al. Prevalence of specific depressive symptoms was calculated for both the vascular and non-vascular groups. Next, prevalence of vascular risk-factors was calculated for subgroups of patients with specific depression symptoms, which would be more prevalent in 'vascular depression': anhedo-

nia and psychomotor change. A logistic regression analysis was carried out controlling for confounding effects of the significant differences found in the bivariate analysis.

7.5 RESULTS

7.5.1 General characteristics of the study groups (table 1)

In the AMSTEL study we identified a total of 523 subjects who fulfilled the diagnosis of depressive disorder according to the AGECAT system ('depressive caseness'). Two-hundred and twenty of these fulfilled vascular criteria (42%). The vascular subgroup differed from the non-vascular in that there were more males (chi-square = 21.910, df 1, $p<0.001$) and they had lower scores on the I-ADL measure (t=63.292, df 1, p=0.04). In the Rotterdam Study, we identified 333 subjects with depressive symptoms (cut-off score on the CES-D $\geq$ 16). Of these, 167 fulfilled vascular criteria (50%). In this group the subjects in the vascular subgroup were older (t=577.086, df 1, $p<0.001$), more males (chi-square =7.656, df 1, p=0.006), had more impairments on ADL (t=3.406, df 1, p=0.014) and I-ADL scores (t=137.761, df 1, p=0.011).

In both studies, no differences were found in prevalence of major or minor depressive disorder, nor were there any differences in total number of depressive symptoms, number of mood or motivation symptoms.

7.5.2 Clinical profile of vascular and non-vascular depression

The prevalence of DSM-IV depressive symptoms in both the vascular and non-vascular depressed subjects of both community studies are shown in table 2. Both in the AMSTEL and the Rotterdam study subjects in the vascular subgroup showed more loss of energy (Amstel: chi-square=4.138, df 1, p=0.04; Rotterdam study: chi-square=4.709, df 1, p=0.03). In the Amstel study, subjects in the vascular subgroup also showed more appetite disturbance (chi-square=4.558, df 1, p=0.03). The mood or motivation profile was of no adjunctive value in distinguishing vascular from non-vascular depression in both study-groups.

7.5.3 Symptom profiles of subjects with and without vascular risk factors

Figure 1 is a bar-chart representing the prevalence of specific depressive symptoms in subjects with and without a vascular risk profile, based on the CIRS. In the total sample of the AMSTEL study (N=4051), 2232 (55%) had, and 1819 (45%) had no vascular risk. Vascular subjects showed more loss of energy (chi-square=21.880, df 1, $p<0.001$) and more appetite disturbance (chi-square=12.629, df 1, $p<0.001$) than non-vascular subjects.

Table 1: Demographic and clinical characteristics of Elderly patients with presumed Vascular and Nonvascular depressive disorder in both ERGO and AMSTEL community study-group.

	The Rotterdam Study					AMSTEL				
	Vascular (N=167)		Nonvascular (N=166)			Vascular (N=220)		Nonvascular (N=303)		
	Mean	SD	Mean	SD	p-value	Mean	SD	Mean	SD	p-value
Age (yrs)	76.5	7.2	73.9	7.6	0.001	75.5	5.7	75.9	5.6	0.36
Sex (%female)	68		82		0.006	73		90		< 0.001
ADL	2.0	0.7	1.8	0.7	0.014	11.0	1.6	11.3	1.5	0.08
I-ADL	21.1	4.7	22.4	4.5	0.011	12.8	3.9	13.5	3.6	0.04
MMSE	26.4	3.0	26.9	3.0	0.18	25.8	4.3	26.0	4.2	0.48
Hamilton score	7.9	5.0	7.5	4.9	0.45					
Diagnosis of major depression (%)	21		19		0.60	33		33		0.99
Diagnosis of minor depression (%)	17		21		0.47	10		11		0.81
Total number of depressive symptoms	2.0	2.2	1.9	2.0	0.81	3.0	1.8	2.8	1.7	0.21
Total number of mood symptoms	0.9	1.1	0.8	1.0	0.27	1.3	1.0	1.2	1.0	0.44
Total number of motivation symptoms	1.1	1.2	1.1	1.2	0.79	1.7	1.2	1.5	1.2	0.23

Depressive disorder is defined as a CES-D score > 16 (The Rotterdam Study) or GMS-AGECAT screen positive (AMSTEL).

7.5.4 Vascular risk-profile in patients with predominant 'vascular depression' symptoms

In table 3, the vascular risk-profile of subjects of the Rotterdam Study with and without certain depressive symptoms is shown. All three symptom-groups were more severely depressed and more cognitively disturbed. Depressed persons with anhedonia used more antidepressant medication than those without anhedonia (chi-square = 10.105, df 1, p=0.001). Depressed persons with loss of energy more often had myocardial infarction and peripheral arterial disease than those without loss of energy (chi-square = 5.241, df 1, p=0.022). No other associations were found. Subgroups of persons with anhedonia, psychomotor change or loss of energy showed similar levels of depression, as measured with the HAMD and also similar levels of cognitive functioning, as measured with the MMSE.

Table 2: Prevalence of individual symptoms of depression in patients with Vascular and Nonvascular depressive disorder

	The Rotterdam Study			AMSTEL		
	Vascular (N=167)	Nonvascular (N=166)	p-value*	Vascular (N=220)	Nonvascular (N=303)	p-value*
DSM-IV mood-item:	%	%		%	%	
Depressed mood	38	33	0.32	51	51	0.96
Loss of interest	37	39	0.70	25	23	0.48
Appetite disturbance	18	14	0.31	20	13	**0.03**
Sleep disturbance	73	71	0.69	51	57	0.20
Psychomotor change	20	25	0.28	32	32	0.90
Loss of energy	39	28	**0.03**	59	51	**0.04**
Feelings of guilt	6	7	0.65	11	11	0.99
Thinking / concentration	14	13	0.86	48	47	0.90
Thoughts of death	26	31	0.35	48	48	0.94

Depressive disorder is defined as CES-D score > 16 (ERGO) or GMS-AGECAT screen positive (AMSTEL).
* Chi-square (Pearson); analysis by logistic regression adjusting for age, sex, ADL and I-ADL in the Rotterdam Study, and for sex and I-ADL in the Amstel study

7.6 DISCUSSION

We found no grounds for a specific symptom profile for depression in subjects with vascular risk-factors in two large population based cohorts. This finding is in line with an earlier

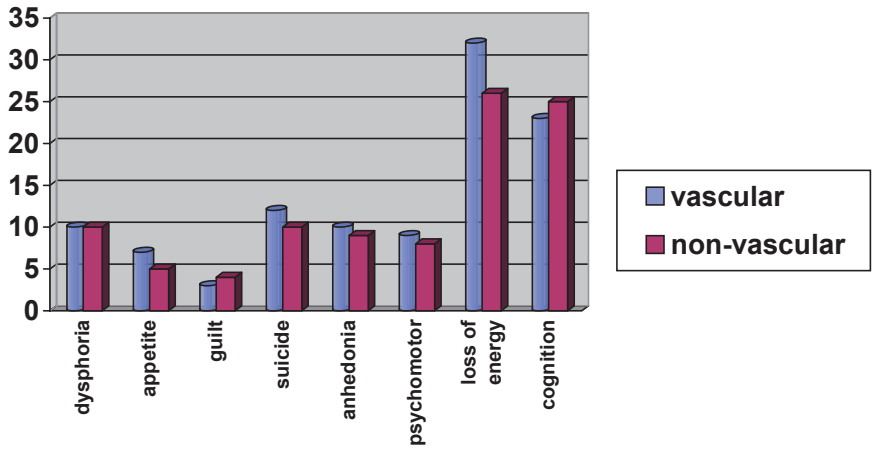

Figure 1: Depression symptoms of vascular and non-vascular subjects of the AMSTEL study.
Vascular subjects had a score of >= 1 on the CIRS; N = 2232; Non-vascular subjects had a score of 0 on the CIRS; N = 1819.

Table 3: Vascular risk characteristics of subjects with and without anhedonia, psychomotor change or loss of energy.

	The Rotterdam Study					
	No anhedonia (N=159)	*Anhedonia (N=87)*	*No psychomotor change (N=196)*	*Psychomotor change (N=50)*	*No loss of energy (N=172)*	*Loss of energy (N=74)*
Characteristic:						
Age, mean (SD), years	73.8 (6.9)	73.8 (7.1)	73.9 (7.1)	73.5 (6.4)	73.5 (7.0)	74.5 (6.8)
Sex, % female	76	71	75	72	73	77
Primary education only, %	61	56	60	57	58	61
MMSE-score, mean (SD)	27.1 (2.6)	26.2 (3.4)#	27.0 (2.8)	26.0 (3.4)#	27.2 (2.2)	25.9 (4.1) †
Hamilton-score, mean (SD)	5.4 (3.4)	11.4 (4.7) †	6.9 (4.9)	9.8 (4.1) †	6.0 (3.6)	11.0 (5.5) †
History of stroke, %	6	8	8	2	7	7
History of MI, %	9	12	11	6	9	19#
Smoking:						
Current smoker, %	18	23	17	28#	20	19
Ex-smoker, %	42	41	44	38	43	42
Antidepressant medication, %	6	20†	11	12	9	16
Blood pressure, mean (SD), mmHg						
Diastolic	72 (11)	74 (13)	72 (11)	76 (13)	74 (12)	71 (12)
Systolic	142 (21)	140 (26)	140 (22)	144 (27)	142 (21)	139 (27)
Total cholesterol, mean (SD) mmol/l	5.8 (0.9)	5.9 (1.0)	5.8 (0.9)	5.9 (1.1)	5.9 (1.0)	5.7 (0.8)
Body Mass Index, mean (SD)	27.1 (4.0)	26.7 (3.9)	26.9 (3.8)	27.0 (4.6)	27.0 (4.0)	27.0 (4.1)
Diabetes Mellitus, %	12	6	11	6	10	10
Common carotid intima-media thickness, mean (SD), mm	0.88 (0.16)	0.90 (0.16)	0.88 (0.15)	0.91 (0.17)	0.88 (0.15)	0.88 (0.17)
Peripheral arterial disease*, %	23	22	24	15	18	31#
Carotid plaques, %						
None	29	28	28	28	28	29
Mild	17	18	16	21	16	19
Moderate	33	35	35	28	35	31
Severe	22	20	21	23	21	21
Aortic calcifications, %						
None	18	16	18	15	17	16
Mild	30	33	32	27	29	34
Moderate	28	17	22	34	29	15
Severe	25	34	29	24	25	34

Abbreviations: MI, myocardial infarction; MMSE, Mini-Mental State Examination

* defined as an ankle-brachial blood pressure index below 0.9.

# $p < 0.05$; † $p < 0.001$

Continuous variables were analyzed by analysis of covariance using t-test, and categorical variables by logistic regression, adjusted for age, sex, Hamilton and MMSE scores when appropriate.

Numbers of aortic calcifications were 212 in all three groups, for carotid plaques 237. Group percentages did not differ significantly from the total group that was screened and no correlation was found between severity of aortic calcification or carotid plaques in any of three groups (Spearman's rho).

study on the vascular depression hypothesis in the community (Licht-Strunk et al. 2004).

The two presumed specific symptoms of vascular depression, anhedonia and psychomotor disturbance, were not any more prevalent in the vascular than in the non-vascular subjects in either of the two cohorts. We found that depressed persons with an increased vascular risk showed more loss of energy in both cohorts, and in the Amstel cohort this vascular depressed group also showed more appetite disturbance. Loss of energy and appetite disturbance was associated with vascular risk-factors in the Amstel study irrespective of concomitant depressive disorder. Also with the use of a more extensive set of vascular risk measures in the Rotterdam Study, no relation was found between the presumed specific symptoms of vascular depression, anhedonia and psychomotor change, with these specific vascular risk-factors, except for the finding that subjects with psychomotor change were more 'current smokers' than those without. The symptom 'loss of energy' was particularly associated with myocardial infarction and peripheral arterial disease.

This association of vascular risk and loss of energy was also found by Licht-Strunk et al. (2004) and in addition, like in our study, depressed subjects with vascular risk showed more disability as measured with ADL and I-ADL scales. Sato et al. (1999) suggested that the functional consequences of cerebrovascular disease may be the causal pathway by which basal ganglia and non-basal-ganglia lesions are associated with depressive symptomatology.

Many studies have been conducted on the subject of vascular depression. They address the relationship of vascular lesions in the brain and depression, a specific symptom profile of vascular depression or the age-of-onset as a specific marker of (vascular) depression. The vast amount of literature illustrates the ongoing debate around the vascular depression concept. Level of caseness, depression diagnosis and referral bias are the major factors that affect findings and conclusions of different studies.

By using two large community studies we have tried to overcome the problem of referral bias. We strictly followed the definition of vascular depression according to Alexopoulos, by studying only subjects who fulfilled criteria for major depression and combining this with scores on the CIRS. Because of the fact that our study did not support the literature on vascular depression and the probability that this could be caused by differences in level of caseness of both depression and vascular risk, we have subsequently analyzed our study groups with different definitions of both depression and vascular risk. Regarding the diagnosis of depression we applied various definitions including 'depressive caseness' (AGECAT / Amstel), major and minor depression and special symptom profiles. None of these had a major effect on the results. We think that for general practice our use of 'depressive caseness' (Amstel) and screen-positive subjects (CES-D $\geq$ 16, Rotterdam Study) was more appropriate because these are the subjects that might consult their General Practitioner with their depressive complaints. Regarding the definition of vascular risk

the CIRS may not be sensitive enough for use in general practice. However, our subdivision into two groups with or without vascular risk factors and a third group with evident vascular disease also did not significantly change our main results. Moreover, the mean scores on the Hamilton Depression Rating Scale in each symptom-group shows that there are no major differences in depression severity between the three symptom-groups.

Some authors have focused on the concept of apathy rather than on depression after stroke, stating that the vascular "depression" actually concerns apathy rather than depression (Starkstein et al. 1993). Apathy is defined as the absence or lack of feeling, emotion, interest or concern which expresses itself in emotion, behavior or social interaction (Marin 1990). It was found to co-occur with depression as a consequence of stroke and is also found in other neuropsychiatric diseases like Huntington and Parkinson disease. It has also been found as a consequence of stroke, without co-existing depression (Starkstein et al. 1993). It has been stated that apathy results from impaired neural processing of novel events caused by dysfunction of the frontal-subcortical system, for example by vascular defects in these regions (Yamagata et al. 2004). New syndromes like the 'depressive-executive dysfunction syndrome' (DEDS), in which the core symptoms are psychomotor disturbances, loss of interest and a mild vegetative syndrome have been released, by Alexopoulos, and several others (Alexopoulos et al. 2002; Vataja et al. 2005). Subjects with this syndrome demonstrate multiple defects in neuropsychological functioning; they show impaired results on tests of fluency, visual naming, abstract thinking, planning, executive complex behavior and concept shifting. This DEDS was also found to be more common in subjects with brain infarcts that affected the fronto-subcortical pathways in some way (Vataja et al. 2005) and it is suggested that in this syndrome dopamine agonists could be helpful in relieving the 'depressive' features (Alexopoulos 2001).

Krishnan et al. have shown that especially apathy was more prevalent in subjects with a late-onset of the depression as compared to those with an early-onset, although they state that it is hard to demarcate these two groups from each other (Krishnan et al. 1995).

Our results do not definitively disprove the concept of vascular depression. A 'vascular' etiology of the depression is probably associated with a more chronic course of the depressive disorder (Mast et al. 2004a) and might be a predictor for poor response to antidepressant medication (Fujikawa et al. 1996). It is also associated with poor outcome as indicated by higher levels of mortality, higher incidence of new vascular events and higher incidence of subsequent cognitive decline (Baldwin et al. 1993; Penninx et al. 1998b; Penninx et al. 2001; Pohjasvaara 2002). What remains is the challenge to detect subjects with a vascular risk in the general population. The clinical features of these subjects are still ill defined and not very specific. Better use of refined psychiatric tools with emphasis on dimensional rather than syndromal diagnosis could be of great importance to detect special subgroups of subjects with depression, for example those with vascular damage of the brain. Furthermore, not only vascular changes are of importance in

provoking depressive symptoms and signs in (elderly) subjects suffering of a vascular burden; external motivation for depression can not be denied and for psychiatry the challenge remains to come to a full understanding of biological and social determinants of behavior and their interaction (Kandel 1998).

Chapter 8

General Discussion

This thesis addresses the relationship between depression and vascular risk factors in general and vascular damage of the brain more specifically. The main focus is on symptom profiles of depression. In this general discussion, I will first start with a summary of the most important findings of the studies described in this thesis. Next, I will discuss some methodological and conceptual issues that are important for an accurate interpretation of the findings and determination of their clinical relevance. The key-concepts in this will be 'complex disorders' and 'levels of explanation'. Finally, I will outline my suggestions for future research on this topic.

8.1 SUMMARY OF THE MAIN FINDINGS

8.1.1 Disease-specific properties of depression rating scales in patients with stroke. (Chapter 2)
The Hamilton Rating Scale for Depression (HAMD) is often used in research into post stroke depression (PSD). Although this rating scale was originally designated to measure the severity of depressive disorders, it is often used for diagnostic purposes in PSD research. We have studied the psychometric properties of this rating scale for three different diseases of the brain, stroke, Alzheimer's disease (AD) and Parkinson disease (PD). We found that the concurrent validity of the HAMD with the DSM-IV criteria of major depressive disorder was high in each of these groups, but that the use of this scale in patients with stroke or another organic brain disease will require the application of disease-specific cut-off scores for screening, diagnostic and dichotomization purposes. These disease-specific cut-off scores were highest in PD and lowest in stroke patients, and those of AD patients lay in-between.

8.1.2 Depression in vascular dementia: phenomenology and association with fronto-subcortical dysfunction. (Chapter 3, 4 and 5)
In patients suffering from vascular dementia, affective disturbances are often encountered, probably more often than in Alzheimer's disease (Newman 1999). It has been suggested that the nature of symptomatology can help to distinguish organic from psychological depression. Vascular depression is defined as having more psychomotor disturbance and more loss of interest (anhedonia). In our study on vascular demented subjects we have used the subdivision of Forsell et al. (1993), who described 'low motivation' and 'low mood' syndromes in demented, depressed subjects. Patients with predominantly 'motivational' symptoms are more likely to have an organic etiology for their depression. The specific features of these subsyndromes are:

- Mood disturbance: dysphoria, feelings of guilt, thoughts of death and appetite disturbance.
- Motivational disturbance: loss of interest, psychomotor change, loss of energy and thinking or concentration disturbance.

In our clinical group of patients from a specialised stroke-unit we have assessed the interrelationship of depression and dementia post-stroke. A principal component analysis of the psychiatric symptoms and signs revealed three distinct sub-syndromes: one with predominantly mood symptoms, one with essentially psychomotor symptoms, and one with vegetative symptoms. Mood, psychomotor and vegetative symptoms were all independently and strongly related to the diagnosis of major depressive disorder according to DSM-III-R criteria. Moreover, the psychomotor factor was the only factor that was also firmly associated with dementia. In a further analysis we have tried to unravel whether

the relationship between the affective and cognitive features of these patients is mediated by fronto-subcortical dysfunction. Associations were computed between measures of depressive symptoms and a comprehensive set of neuropsychological tests. Our hypothesis was supported by a negative correlation between scores on the Verbal Fluency Test and the total number of motivational depressive symptoms. None of the neuropsychological tests was significantly related to the number of mood symptoms nor did they correlate with the total number of depressive symptoms. The results indicate that different dimensions of depression can be discerned in a group of patients with vascular dementia and that the symptom profile of depression in these patients can be affected by the presence and severity of dementia and especially by fronto-subcortical dysfunction.

8.1.3 Symptom profiles in subjects with vascular risk-factors in the general population. The "vascular depression" concept. (Chapter 6 and 7)

If specific symptom profiles of depressive disorders in the elderly are related to a specific etiology, this could have implications for everyday clinical practice. The vascular depression hypothesis states that especially in the elderly a sub-type of depressive disorder exists that is caused by vascular brain disease. Subjects with a vascular risk would show more anhedonia, psychomotor change and less feelings of guilt, than subjects without a vascular risk. In the first place, this hypothesis was tested by comparing the symptom profiles of subjects in the general population with predominantly vascular, degenerative or inflammatory risk factors. Motivational symptoms were associated with vascular or degenerative risk-indicators for depression; psychomotor change with both indicators; loss of energy with the vascular, but also with the inflammatory indicator and thinking/concentration disturbance with the degenerative indicator. The so-called mood symptoms of depression, especially thoughts of death, and melancholic symptoms like appetite and sleep disturbances were more strongly related with the inflammatory risk-indicator. From this study it can be concluded that in patients with a late-life depression, specific symptoms of the depressive disorder may reflect the predominant underlying pathogenic mechanism, but next to the symptoms of loss of interest (anhedonia) and psychomotor disturbances, loss of energy (lassitude) and appetite disturbance may be important in the vascular profile. To further test the vascular depression hypothesis, we have studied the phenomenological characteristics of subjects with and without vascular disease and with and without depressive disorder in the open population.

The main findings were that we could not confirm the specific symptom profile of vascular depression with predominant anhedonia and psychomotor disturbance. Neither of these were more prevalent in the vascular groups than in the non-vascular groups of both our population-based studies. We did find that depressed persons with a vascular risk showed more loss of energy in both study-groups, and appetite disturbance in the other. Conversely, we found that the presumed specific symptoms of vascular depression,

anhedonia and psychomotor change, did not have any relation with specific vascular risk-factors, except for the finding that subjects with psychomotor changes were more 'current smokers' than subjects without psychomotor changes. Loss of energy was associated with myocardial infarction and peripheral arterial disease. In the total group of subjects, including depressed as well as non-depressed subjects there were also associations between the symptoms loss of energy and appetite disturbance and the group with vascular risk.

8.2 METHODOLOGICAL AND CONCEPTUAL CONSIDERATIONS

In this section, the methodological strengths and limitations of the way the various studies were designed are discussed and some conceptual considerations are outlined.

8.2.1 Symptom profiles of depression

As stated in Chapter 1, it is necessary to use adequate and well-known measures of depression to allow meaningful interpretations of the research findings. However, the main aim of this thesis was to determine distinct symptom profiles for subjects with vascular risk or vascular brain damage. We therefore chose to follow a parallel route. We did not only use the established classification system to come to the detection and classification of major and minor depressive disorder, but we also applied a dimensional approach, based on the reports from Forsell, Alexopoulos and Krishnan (Forsell et al. 1993; Alexopoulos et al. 1997b; Krishnan et al. 1997). Forsell has subdivided demented subjects with a depressive disorder into subjects with predominant mood and predominant motivational disturbances. The mood profile consisted of psychological, or 'positive' symptoms of depression like dysphoria, negative thoughts, guilt feelings and suicidal ideation. The motivational profile on the other hand consisted of an apathy-like syndrome, or 'negative' syndrome with loss of interest (anhedonia), psychomotor retardation and indecisiveness (Forsell et al. 1993). Especially the motivational profile not only has much in common with the concept of apathy (Marin 1990) but also with the symptom profile of vascular depression, as defined by Alexopoulos and Krishnan (see also Chapter 1) (Alexopoulos et al. 1997b; Krishnan et al. 1997). No specific instruments are available for the measurement of these new dimensional concepts. Moreover, because we used different groups of subjects for our analysis, measurement of depression was done by using various methods. For Chapter 2, 3 and 4 the affective part of the Schedule for Affective Disorders and Schizophrenia (SADS) was used to elucidate all depressive symptoms (Endicott & Spitzer 1978). The SADS is a semi-structured interview, which enables the confirmation of the diagnosis of major depressive disorder according to DSM-IV-criteria (APA 1994). In the Nijmegen and Amstel study, diagnosis of depression was made according to the

GMS-AGECAT system (Copeland et al. 1986; Copeland et al. 1988). The Dutch language version has proven reliability for epidemiological work in replication studies (Hooijer et al. 1991). Finally, in the Rotterdam Study diagnosis of depression was assessed by a two-step procedure. First, participants completed the Dutch version of the Center for Epidemiological Studies Depression Scale (CES-D). A score of 16 was used as a cut-off to indicate depressive symptoms (Beekman et al. 1997b). In a second step, screen-positive subjects were studied with the Dutch version of the Present State Examination, a semi-structured psychiatric interview included in the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO 1997).

All instruments not only diagnose major and minor depression but also shed light on milder depressive symptomatology, enabling emphasis on dimensional instead of syndromal properties. This is one of the major strengths of this thesis. As a matter of definition, incomplete depressive disorders are more common than the category of major depression. This 'level of caseness' is of major importance for the results. The application of stricter criteria for depression will weaken the association found between physical illness and depressive disorder and thus, subjects with a vascular risk or with a PSD have strong associations with certain symptoms (for example: psychomotor changes), a milder association with a certain profile (the motivation profile) and the weakest association with an affective syndrome according to DSM-criteria (major depression). This was confirmed by our findings. The same might be true for the cognitive features and as a result, findings on co-morbidity of affective and cognitive disorders in post-stroke subjects or subjects with a high vascular risk, are also strongest at the symptom-level and will probably weaken when stricter criteria for both depression and dementia are applied. As a matter of fact, applying a more sophisticated concept of depression or dementia on these subjects instead of just affective or cognitive symptoms or signs is more in line with the complex reality. Looking at only symptoms and their relation with vascular lesions is just one piece of the complex puzzle and only addresses one level of explanation (see paragraph 8.2.2).

We could not address the question of specific localisation that would render specific symptoms or symptom profiles, but this still remains interesting. Apart from specificity of localisation the factor of vascular load has been introduced (Krishnan & McDonald 1995). A critical level of damage to certain systems in the brain should be reached to bring about depressive symptomatology (also known as the redundancy effect). The systems at play would be fronto-subcortical systems, which are norepinephrine systems. Damage therefore will lead to reduced norepinephrine turnover and this will induce depression-proneness in these subjects. Others have mentioned a 'built-up' of symptoms in a hierarchical way (Parker et al. 2003). Mood features would be followed by psychomotor features and eventually, psychotic features could complete the major depressive disorder.

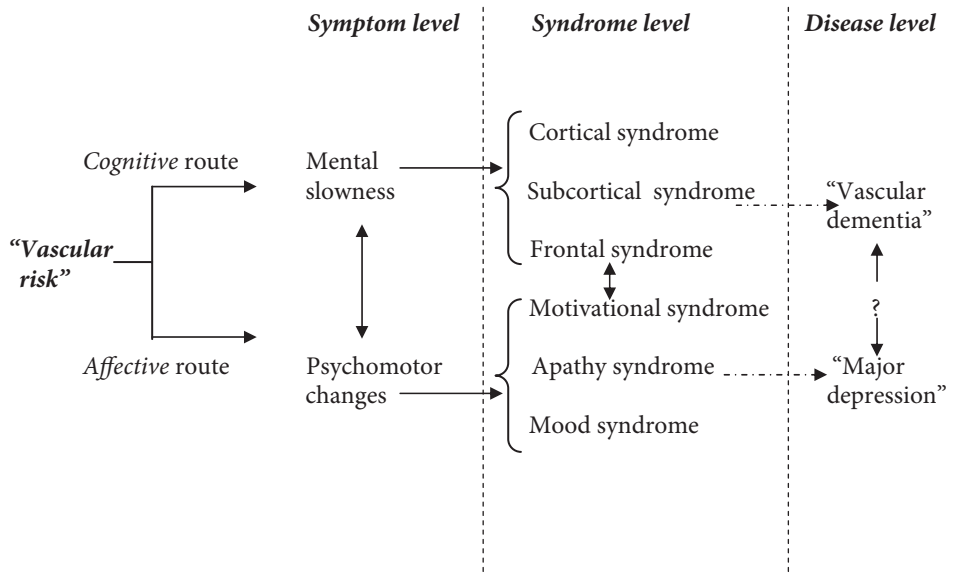

Figure 1: Level of caseness and inter-relationship of cognitive and affective features following cerebrovascular lesions

8.2.2 Levels of explanation

At first, the clinical discovery of PSD has evoked a lot of research and has fuelled the long existing dissension on organic and functional disorders. In earlier days, organic psychiatric disorders were defined by a clear neuropathological substrate. An example for this is Parkinson disease, in which selective neuronal loss leads to comprehensible clinical phenomena. Functional disorders, like schizophrenia, did not have such a substrate. In modern times, the extra connotation given to a functional disorder is that it merely pertains disturbances of function, which can be induced by psychosocial factors. Divergent concepts like this were the logical consequence of Cartesian dualism and have prevailed for a long time in psychiatry. With the upcoming psychopharmacology, neurobiology and structural and functional brain imaging techniques, knowledge about the pathophysiology of mental disorders has been boosted enormously. It is now clear that all mental processes are the result of neuronal processes in the brain, and mind and brain are commensurable. The distinction between mind and brain has been a hindrance for scientific progress (Kandel 1998). Human first-person world of experience might be unique but it emerges from and is total dependent upon brain function, although on the other hand, brain function can be a reaction to social and cultural processes. Thus the mental (functional) and biological (organic) become different levels of viewing the same subject (circular interaction). A risk of these new insights is that in research the significance of biological factors is exaggerated, as some have stated that psychiatry cannot be too biological (Guze 1989). Biological reductionism is certainly a risk that is involved in

this thesis too. Although the precipitation of depression by stroke as in PSD suggests a causal relationship, not all subjects suffering from stroke will develop PSD. The same is true for elderly subjects with vascular risk factors; not all subjects with a major vascular risk will develop a depression. As was stated before, most psychiatric disorders are of the complex type, which means that no single cause will be responsible. The new philosophical structure that has to be set in psychiatry has to contain some major propositions (Kendler 2005):

1. Psychiatry is irrevocably grounded in mental, first-person experiences.
2. Cartesian substance dualism is false.
3. Epiphenomenalism is false.
4. Both brain-mind and mind-brain causality are real.
5. Psychiatric disorders are etiologically complex.
6. Explanatory pluralism is preferable to monistic explanatory approaches, especially biological reductionism.
7. Psychiatry needs to move from a prescientific "battle of paradigms" toward a more mature approach that embraces complexity along with empirically rigorous and pluralistic explanatory models.
8. Accept "patchy reductionism" with the goal of piecemeal integration in trying to explain the complex etiological pathways to psychiatric illness a little bit at a time.

An elegant example of this approach is delivered on the complex relationship between depression and mortality by Schulz et al. (2002) (fig. 2). Not only will behavioural risk factors increase the risk of developing depression, but moreover, they will increase the risk of developing other (sub)clinical diseases, for instance vascular brain disease and thus contribute to an increased risk of death. The authors not only address plain cerebrovascular and other somatic illness but also lifestyle factors, stressing the inter-relationship of these factors.

The results of this thesis thus can contribute to a part of the complex, explanatory, etiological pathway that leads to the development of PSD or vascular depression. There will be lots of small explanations, from a variety of explanatory perspectives, each addressing a part of this complex disorder. These etiological pathways will not be simple, linear and one-way interactions, but complex and interacting, like networks. The basic attitude that is needed is explanatory, integrative pluralism. In PSD and vascular depression some of the pieces of the puzzle will be for instance: (a) Predisposition of men to depression by foetal undernutrition, stressing an environmental factor in early life which could influence the programming of the hypothalamic-pituitary-adrenal (HPA) axis (Thompson et al. 2001). (b) Impairment in executive functioning and attention in patients with a late-life depression, suggesting involvement of specific neuronal circuits (Lockwood et al. 2002; Rapp et al. 2005). (c) One of the latest replication studies on the relationship between white matter hyperintensities and depressive features (the level of the brain

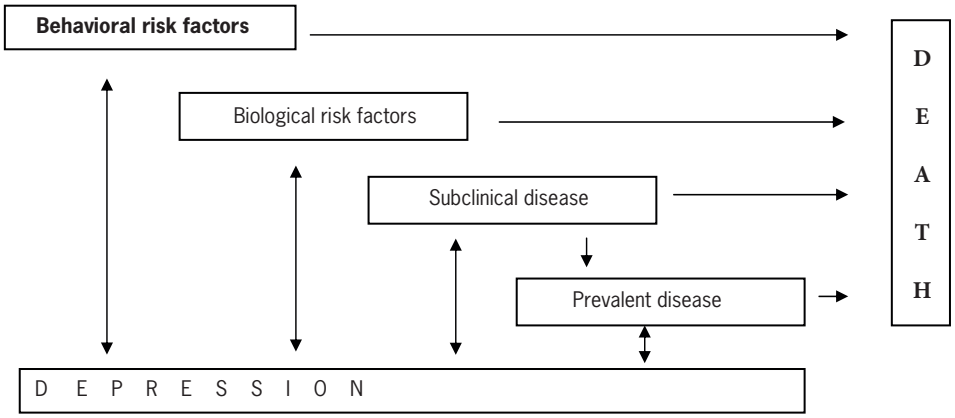

Figure 2: Complex interrelationship between depression and mortality (Schulz et al. 2002)

and brain function) in mid-adult life stresses the importance of the mediating role of physical disability in this association (the level of the social system) (Jorm et al. 2005). (d) The prediction of shorter time to remission by greater intrinsic religiosity, pointing at a transcendent factor that might influence the subjective suffering from depression (Koenig et al. 1998).

8.2.3 Statistical issues

Some of the statistical methods used in this thesis need some extra comment. In this paragraph these comments will concern (1) ROC-curves, (2) factor analysis, (3) data imputation and (4) specificity of symptoms.

8.2.3.1 ROC curves

In order to determine and compare the sensitivity and specificity of a diagnostic instrument and to obtain optimal cut-off scores, we plotted 'receiver operating characteristic'

Level	Research findings
Molecular / DNA	Genetic alterations, linkage disequilibrium and association of certain DNA profiles with endophenotypes
Cellular / Neurotransmitters	Altered levels of neurotransmitters, cellular degeneration or dysfunction
Brain structures / Neuronal circuits	Localised functions, neuropsychological deficits
Whole brain / Organism	Unique personal experience: psychiatric features and phenomena including somato-visceral symptoms
Social system / Family, work etc.	ADL and I-ADL shortcomings, interaction problems with spouse, family members, change of roles
Cultural and transcendental systems	Specific elements in art, religion, folklore and rites

Figure 3: Levels of explanation

curves (ROC curves) (Murphy et al. 1987). These curves yielded the 'sensitivity' versus '1 minus the specificity' for every possible cut-off point. The optimal cut-off point was determined visually by assessing which score combined maximum sensitivity with optimal specificity. The area under the curve (AUC) is an indicator of the ability of the scale to distinguish between depressed and non-depressed patients. Optimal cut-off scores were determined for each group of patients, including cut-off scores that could be used for a screening, diagnostic and dichotomization (i.e. discriminating depressed from non-depressed patients) purposes. In order to determine whether the HAMD could be used as a predictive test for these three groups of patients, positive predictive (PPV) and negative predictive values (NPV) were calculated for different cut-off scores in the central range of the scale. The validity of the ROC curves can be compared in pairs with the Hosmer-Lemeshow goodness-of-fit test (Hosmer et al. 1988). The major problem of using these kinds of statistics is that they involve the risk of circular reasoning. It can be argued that one should not use the DSM-criteria as the golden standard in these somatic disorders, because various somatic and psychomotor symptoms should not be counted as depressive features and therefore wrongfully account for the major part of depressive symptom score on the HAMD. However, there are no more suitable alternatives for the golden standard diagnosis and as a matter of fact, our results did show that this concern is more a theoretical than a clinical / practical problem, because higher scores had a high predictive value for depression in all three groups of patients. In theory, it still remains possible that some patients do have a high score on the HAMD, but will not suffer from one of the key-features of depression, i.e. depressed mood or anhedonia. Therefore, some authors have stated that depression only could be diagnosed when a minimum score on the HAMD was reached and if one of these key-features is present (Leentjens et al. 2003).

8.2.3.2 Factor and discriminant analysis

The primary aim of a factor analysis is to obtain a data reduction and to uncover underlying structure of the data. The purpose of data reduction is to remove redundant (highly correlated) variables from the data file, perhaps replacing the entire data file with a smaller number of uncorrelated variables. The purpose of structure detection is to examine the underlying (or latent) relationships between the variables. There are several assumptions to be made, before one should apply this statistical method to the available data. One should know how many factors are needed to represent the variables and what these factors will represent in the population under study. We have chosen the method of Forsell et al. (1993) who had found two distinct symptom clusters of depression in a group of demented subjects.

The factor analysis that we used in this thesis is a principal component analysis with varimax rotation. We were looking for dimensional clusters of symptoms that would

correlate with neurobiological markers and unlike the prevailing cluster(s) of the DSM-classification, similar to the earlier findings of Forsell. Symptoms were added to a factor when factor loading was greater than .40, which is arbitrary, but common practice in factor analysis. Because our findings supported the earlier findings the study could be considered a replication, although in another group of subjects. Therefore, the procedure is, although precarious, justified.

8.2.3.3 Data imputation

Imputation of data means the replacement of missing values in the dataset. Missing data can be due to multiple causes. In our study-group we were confronted by a large proportion of subjects that were not able to participate in neuropsychological testing, while this was our main topic of interest (chapter 4). In this study we replaced values only due to cognitive/behavioral disturbances by the worst performance in this study group on that particular test, assuming that these subjects belonged to this worst group of subjects. To determine the effect of the adjustments, the so-called effect size can be computed for each test variable. This is calculated by the difference between the observed and the adjusted means divided by the observed SD. An effect size of 0.8 SD should be considered as large, of 0.5 SD as medium and an effect size of 0.2 SD as small (Cohen 1988). We performed a sensitivity analysis to check whether imputation with the average score on the test or a score in between the worst and the average (25th percentile) would alter the correlation coefficients between the measures of depression and the neuropsychological test scores, but it did not. Although these methods have been used elsewhere before and have proven to be reliable, the amount of missing data in our study suggested that most of the neuropsychological tests were of no use in this study-group and thus imputation remains precarious. Unfortunately, no specific neuropsychological (frontal) test is applicable to all patients in such a severely ill study-group. Nevertheless, newer test should be developed, enabling the adequate measurement of frontal functioning in this category of patients. For this thesis, although with shortcomings, no better solution was within reach.

8.2.3.4 Specificity of symptoms

In chapter 6 and 7 we have tried to find specific symptoms of depressed subjects with vascular risk factors or vascular disease. The only significant association that was found concerned the symptom of loss of energy. Statistical significance, however, is not equal to clinical significance. Only when a symptom or marker has a very high specificity will a positive finding rule in the diagnosis (of vascular depression). Similarly, when a symptom or marker has a very high sensitivity, a negative result will rule out the diagnosis. The Likelihood-ratio is calculated by dividing the chance that someone with a marker has the disease by the chance that someone without this marker has the disease. The likelihood ratio incorporates both the sensitivity and specificity of the test and provides

a direct estimate of how much a test result will change the odds of having a disease. The likelihood ratio for a positive result (LR+) tells you how much the odds of the disease increase when a test is positive. The likelihood ratio for a negative result (LR-) tells you how much the odds of the disease decrease when a test is negative.

Specificity of lassitude for vascular risk in the total, general population is only 48%, combined with a sensitivity of 61% giving a positive Likelihood-ratio (LR+) of only 1.15. When we do this analysis on the depressed subgroup in the general population, specificity rises to 60%, but sensitivity is only 50%, leading to a LR+-ratio of 1.22, which is also not a very useful result for everyday practice. The post-test probability will only rise from 50% to 54%. We could not analyse such symptom-specificity in our clinical groups, because we only had clinical subjects with a vascular disease of the brain and no non-vascular group to compare with. These calculations lead us to the conclusion that we need more markers or a set of markers to come to a satisfactory predictive profile for clinical practice.

8.2.4 Data-resources

The subjects under study in this thesis were from various sources. For the study on the validity of the HAM-D subjects of different clinical trials were used. In the study on depressive symptoms in vascular dementia and their relationship with neuropsychological dysfunction subjects from a clinical stroke-unit were used. Finally, for associations of vascular risk factors with the depression symptom profile we used data out of two large community studies. Because the information out of different resources is supporting the same hypothesis, this is a strong point of this thesis. On the other hand a major shortcoming is that, being data from various sources, this makes them at some point incomparable.

As was stated in the introduction, clinical and community studies both have their own methodological problems. Inherent to all community studies, participation rate can be a problem; although in both our community studies, the participation rate was acceptable, attrition is still a risk. This would mean that the most severely-ill subjects dropped out of (or: did not enter) the study, which could weaken the possible association between vascular risk-factors and depressive symptoms. As a consequence, the real association could be stronger than the one we found in this study. In clinical studies, especially those in tertiary settings, only the most severely ill subjects will enter the study. This selection-bias would mean that a stronger relation is found in the study than in reality exists. In our clinical study, the selection was made only concerning the cerebrovascular illness. Although the Rotterdam Stroke Databank was designed to non-selectively include all consecutive stroke patients, referral to this stroke-unit was differential in that younger subjects and subjects with a presumed, rare cause of stroke were overrepresented. This might have influenced our results, although the direction of this influence is not certain.

8.3 CLINICAL RELEVANCE

8.3.1 Transference to clinical practice

1. Diagnosis of depression in patients who suffered from a stroke can be difficult. Overlap of physical symptoms with melancholic or autonomous symptoms of depression can be a problem, although in comparison to Alzheimer's and Parkinson's disease, this is less a problem in stroke. Rating scales like the HAM-D can be of help for both screening and diagnostic purposes, unless one uses the appropriate cut-off scores as recommended in this thesis.
2. In a specialised stroke unit, we found that the depression profile is associated with the cognitive state of the patient. Subjects with more cognitive deterioration show more motivational symptoms. This association is likely to be mediated by frontal-subcortical dysfunction, although in severely demented patients, this function is difficult to measure.
3. In the general population our results do imply that certain profiles of depression, especially in the elderly, indeed might be a predictor of vascular brain disease or even vascular dementia. Our findings are not conclusive on specific symptom profiles of depression in subjects with vascular risk or vascular brain disease. It is a risk that GPs by all means should be aware of, when elderly subjects with no psychiatric personal history present themselves with depressive complaints, especially when other vascular risk factors are at hand.

8.3.2 Clinical relevance of these findings

The association of cerebrovascular disease and depression has been a subject of interest for a long time. Both PSD and vascular depression have been studied extensively. In this thesis we have tried to find further support for a specific clinical psychiatric presentation of the affective disturbances. We found additional evidence for the existence of such a specific clinical presentation, although these findings were much weaker in the general population than in our clinical sample. Our findings suggested that in vascular disease of the brain the prominent symptoms of depression are the so-called 'motivational' symptoms, such as loss of interest (anhedonia), psychomotor changes, loss of energy (lassitude) and thinking / concentration disturbances. In the general population this association was much weaker and actually remained significant only for the rather non-specific symptom of lassitude. This would mean that there indeed might be a kind of vascular gradient and that the more severe the vascular disease of the brain is, the more evident this vascular depression profile will manifest itself, probably in cohesion with cognitive decline. For clinical practice, this means that in everyday practice, no clear clinical profile can be given to easily recognize the depressed patient with a vascular risk, although with promi-

nent lassitude, there is a higher risk. If one would like to use such a symptom as a marker for vascular risk, it should be specific for this risk, which is not the case.

8.4 FUTURE RESEARCH

As was outlined in paragraph 8.2.2 psychiatric research can only be helped forward by explanatory pluralism. Searching for and developing one final theory is attractive but also unrealistic. In a structure of overlapping findings from research on different levels of explanation, we will probably be able to come to a piecemeal integration and finally to a full causal network for vascular and post-stroke depression. In the field of first-person phenomenology this will mean that further clarification and definition of different dimensions of depression is still of major importance. Linkage of these dimensions to other levels of explanation, like the neuropsychological, neuronal circuitry level or the functional-anatomic brain level still has to be elaborated. Next, an important clinical implication could be that specific treatment modalities can be studied in clearly-defined subgroups. This would imply for instance investigating whether a group of stroke patients with predominant motivational or apathetic symptoms would benefit from specific interventions, for instance serotonergic antidepressants or maybe even dopamine-enhancing medications like buproprion. The same kind of study would be interesting in elderly subjects with presumed vascular depression with predominant motivational and apathetic symptoms. Thus, new studies would need a very strict psychiatric diagnostic procedure, again not only addressing DSM-categories, but also apathy, mood and motivation sub-syndromes. A thorough neuropsychological evaluation will render more firm data, which could be correlated to the psychiatric findings. Correlation with new, more detailed and functional neuro-imaging data would complete the study and so this study could contribute to the understanding of how neuronal circuits work together in the development of depressive disorders in men and give support to evidence-based treatment of PSD and vascular depression.

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Samenvatting

(summary in Dutch)

INLEIDING

Dit proefschrift gaat over de klinische verschijningsvorm van depressie bij personen met cerebro-vasculaire stoornissen. Enerzijds betreft het depressies die ontstaan na een beroerte (ook wel aangeduid met cerebrovasculair accident of kortweg CVA), anderzijds ook depressies die optreden bij personen die in meer of mindere mate vasculaire risicofactoren hebben of bij wie op MRI of CT-scan aanwijzingen zijn voor doorbloedingsstoornissen van de hersenen. ***Hoofdstuk 1*** geeft achtergrondinformatie over dit onderwerp. Achtereenvolgens wordt eerst algemene informatie over depressie, in het bijzonder depressie bij ouderen en over cerebrovasculaire stoornissen gegeven. Daarna worden de mogelijke combinaties van deze twee belangrijke volksgezondheidsproblemen besproken. "Post-stroke depressie" en "vasculaire depressie" zijn twee belangrijke termen die in dit onderzoek gebruikt worden. Beide begrippen worden toegelicht en het onderzoek dat tot op heden hierover is gedaan wordt kort samengevat. De belangrijkste methodologische problemen waarop men stuit bij het onderzoeken van personen met een depressieve stoornis in combinatie met doorbloedingsstoornissen van de hersenen worden daarna uiteengezet. Het gaat daarbij om de volgende vragen: Welke definitie wordt er gehanteerd voor de depressie? Hoe is het tijdsverband tussen de depressieve verschijnselen en de cerebrovasculaire stoornissen? Welke groepen worden er onderzocht en welke andere factoren dan de neurobiologische spelen een rol bij het ontstaan van depressie bij ouderen met bijkomende cerebrovasculaire stoornissen? De volgende vragen staan aan de basis van dit proefschrift:

1. Kan de Hamilton Depression Rating Scale (HAMD) gebruikt worden als diagnostisch instrument bij patiënten met een depressie na een beroerte?
2. Hebben patiënten die een ernstig beroerte hebben doorgemaakt en daarbij een depressieve stoornis hebben, een specifiek symptoomprofiel?
3. Bestaat er een relatie tussen de affectieve en de cognitieve gevolgen van een beroerte?
4. Kan de 'vasculaire depressie' in de algemene bevolking als aparte entiteit herkend worden op basis van het symptoomprofiel?

DE STUDIES

Om bovenstaande vragen te beantwoorden zijn in dit proefschrift data uit uiteenlopende studies gebruikt. Hier wordt in het kort even op deze studies ingegaan.

De ***Dutch Vascular factors in Dementia Study*** betreft een onderzoek bij opgenomen patiënten in een tertiaire, academische setting. De patiënten waren 55 jaar of ouder en hadden bij opname een TIA (met neurologische afwijkingen bij lichamelijk onderzoek), een

cerebraal infarct of een intracerebrale bloeding. Het belangrijkste doel van het onderzoek was om inzicht te verkrijgen in de invloed die een breed scala van vasculaire factoren hebben op andere risicofactoren, eigenschappen van de beroerte zelf en het optreden van dementie na een beroerte. Het onderzoek vond plaats op de afdeling Neurologie van het Erasmus Medisch Centrum te Rotterdam.

De ***Depression in Dementia Study*** is een longitudinale studie die werd uitgevoerd door de afdeling Psychiatrie van het Universitair Medisch Centrum St. Radboud te Nijmegen. De dataverzameling vond plaats tussen 1990 en 1994. Het doel van het onderzoek was om de samenhang tussen dementie en andere vormen van psychopathologie (in het bijzonder depressie) in prospectieve zin te bestuderen. In deze studie werden 91 bewoners van verzorgingshuizen met dementie en 110 bewoners zonder dementie gedurende 12 maanden gevolgd. In die periode vonden 3 gedetailleerde metingen plaats van de psychiatrische status met speciale aandacht voor dementie en depressiesymptomen en neuropsychologische functies. De studie werd gesubsidieerd door de JANIVO stichting.

De ***Amsterdam Study of the Elderly*** (AMSTEL) betreft een groot bevolkingsonderzoek dat plaatsvond tussen 1990-1994. In totaal werden 4051 thuiswonende ouderen in Amsterdam thuis opgezocht door getrainde interviewers. Doel van het onderzoek was het in kaart brengen van een breed scala aan demografische, somatische en psychiatrische gegevens. Het onderzoek gaat uit van de vakgroep psychiatrie van de Vrije Universiteit Amsterdam en is ingebed in het onderzoeksprogramma van het EMGO instituut. Het onderzoek werd financieel gesteund door het S.G.O. programma (Stimulering Gezondheidszorg Onderzoek) vanuit het ministerie van VWS. Dit liep af in 1994. Sindsdien wordt het onderzoek verder gefinancierd via projectsubsidies van o.a. het Nationaal Fonds Geestelijke Volksgezondheid, en N.W.O.

De ***Erasmus Rotterdam Gezondheid en Ouderen*** (ERGO) studie betreft eveneens een grootschalig, langlopend bevolkingsonderzoek. Het onderzoek is gestart in 1990 en momenteel is de vierde follow-up ronde gaande. In dit proefschrift worden data uit de derde onderzoeksronde gebruikt. In het onderzoek zijn alle personen van 55 jaar en ouder uit de wijk Ommoord te Rotterdam betrokken. Doel van het onderzoek is het in kaart brengen van de incidentie en prevalentie van risicofactoren voor chronische ziekten bij ouderen. Het onderzoek gaat uit van de vakgroep Epidemiologie en Biostatistiek van de Erasmus Universiteit te Rotterdam. Het onderzoek wordt financieel ondersteund vanuit het Research Institute of Diseases in the Elderly (RIDE, ZonMW). Additionele ondersteuning voor het depressie-onderzoek werd gegeven door Numico Research BV en voor het arterioscleroseonderzoek door een extra subsidie van NWO, 904-61-091.

ONDERZOEKSVRAGEN

Hoofdstuk 2 beschrijft het onderzoek naar de validiteit van de Hamilton depressievragenlijst (Hamilton Depression Rating Scale, HAMD) bij patiënten met een beroerte. In de dagelijkse praktijk wordt dit instrument vaak gebruikt bij patiënten met een depressieve stoornis. De vragenlijst is ontworpen om bij patiënten bij wie een depressie is vastgesteld een indruk van de ernst van de depressieve klachten te krijgen en om eventueel ook de therapie mee te monitoren. In verschillende onderzoeken naar het vóórkomen van depressie na een beroerte wordt de HAMD ook regelmatig gebruikt, maar dan ook vaak als diagnostisch hulpmiddel. In principe is deze schaal hier niet voor bedoeld.

Van drie onderzoeksgroepen met patiënten met verschillende, cerebrale aandoeningen (beroerte, de ziekte van Parkinson en de ziekte van Alzheimer), waren gegevens van de HAMD en van depressiediagnostiek voorhanden. Met behulp van ROC-curves kon worden vastgesteld welke cut-off score voor de verschillende ziektebeelden gehanteerd zou moeten worden om tot een optimale sensitiviteit en specificiteit te komen. De validiteit van de HAMD bleek voor alle drie patiëntengroepen goed te zijn, waarbij voor elke groep wel een andere, ziekte-specifieke, cut-off score gehanteerd dient te worden. Om de HAMD als diagnostisch instrument in het kader van depressiediagnostiek bij beroertepatiënten te gebruiken, is de optimale cut-off score bij 10-11 punten gelegen.

Hoofdstuk 3 beschrijft het onderzoek dat gedaan werd naar de fenomenologie van depressie bij patiënten met een beroerte die tevens cognitieve problemen hebben (vasculaire dementie). Hiertoe werden 78 patiënten uit de Rotterdamse studie naar vasculaire factoren bij dementie (Dutch Vascular Factors in Dementia study) betrokken in een aanvullend psychiatrisch onderzoek. Het merendeel van deze groep (N=54) kreeg de diagnose 'vasculaire dementie'. Een gedetailleerd onderzoek van de stemming vond plaats met behulp van de Schedule for Affective Disorders and Schizophrenia (SADS). Hierdoor werd niet alleen tot een DSM-classificatie van 'major' en 'minor' depressie verkregen, maar kon ook op symptoom en symptoomclusterniveau nader onderzoek naar correlaties plaatsvinden. Met behulp van een factoranalyse werden drie afzonderlijke factoren verkregen. De eerste factor werd de 'stemmings' factor (stemming in engere zin) genoemd en deze bestond uit de symptomen somberheid, geprikkeldheid, piekeren / tobben, negatieve en suïcidale gedachten en het terugtrekken uit sociale contacten. De tweede factor werd de 'motivatie' factor genoemd. Deze bestond uit psychomotore remming, anergie en een gebrek aan mimiek / een somber uiterlijk. De laatste factor werd de 'vegetatieve' factor genoemd en deze bestond uit anorexie en gewichtsvermindering. Een aantal symptomen bleek niet specifiek voor één van deze factoren en werd om die reden van verdere analyse uitgesloten. Het betrof slapeloosheid, anhedonie en angst. Alle drie de gevonden factoren hadden een sterke correlatie met de diagnose 'depressie', wat niet verwonderlijk is, gezien

het feit dat het in feite subsyndromen van de depressie betreft. Daarnaast werd gevonden dat de motivatie-factor een sterke correlatie vertoonde met de diagnose 'dementie', terwijl zowel de stemmings- als de vegetatieve factor deze correlatie niet hadden. Een aanvullende discriminant-analyse liet zien dat motivationele symptomen inderdaad veel voorkwamen bij zowel depressieve als niet-depressieve patiënten met vasculaire hersenschade (en bijkomende dementie) en dat deze dus een lagere discriminerende waarde hebben dan de stemmingssymptomen in engere zin.

In ***hoofdstuk 4*** wordt de in hoofdstuk 3 beschreven groep nader onderzocht. Wij veronderstelden dat de overlap tussen depressie en dementie bij de onderzochte groep patiënten veelal uit de motivationele symptomen van de depressie bestaat. Daarbij gaat het om een symptoomcluster dat grote overeenkomst vertoont met de fronto-subcorticale symptomen van dementie.We onderzochten of er inderdaad een correlatie was tussen de motivationele symptomen en slecht presteren op die cognitieve tests die de fronto-subcorticale functies betreffen. In het onderzoek waren 54 patiënten met een post-stroke dementie betrokken. Bij allen was naast uitvoerige diagnostiek rondom de stemming ook uitgebreid onderzoek naar de cognitieve functies gedaan. Het betrof een groep van matig ernstig dementerende patiënten, met een gemiddelde score op de MMSE van 19.8 punten (SD 5.0). Van deze groep voldeden 21 (39%) aan de criteria van een depressieve stoornis volgens de DSM-IV. Hoewel een uitgebreide neuropsychologische testbatterij werd afgenomen, bleek een groot aantal van deze patiënten niet al deze tests te kunnen doen. De enige test die bij vrijwel alle patiënten betrouwbaar kon worden afgenomen, was de Verbal Fluency Test (VFT). Deze test wordt in de literatuur beschouwd als een belangrijke maat voor het frontaal functioneren, in het bijzonder voor de zogenaamde 'executieve functies'. In onze onderzoeksgroep bleek een negatieve correlatie te bestaan tussen de score op de VFT en de motivationele symptomen van depressie. Dat wil dus zeggen dat patiënten met een hoge score op VFT (wat duidt op 'goede' executieve functie) minder motivationele symptomen vertonen dan patiënten met een lage score. Dit ondersteunt de hypothese dat er een verband bestaat tussen deze fronto-subcorticale, executieve functies en de motivationele symptomen van de depressie.

Ook in ***hoofdstuk 5*** gaat het om de vraag in hoeverre affectieve en cognitieve symptomen aan elkaar gerelateerd zijn bij patiënten met een beginnende cognitieve achteruitgang. In dit onderzoek zijn 60 patiënten met dementie betrokken uit het Nijmeegse onderzoek onder bewoners van een verzorgingshuis. DSM-III-R criteria van depressie werden onderverdeeld in 'stemmings' en 'motivatie' symptomen. Het is opvallend dat 77% van de depressieve symptomatologie bij deze groep bestond uit de 'motivationele' symptomen, meestal buiten de context van een depressieve stoornis. Daarbij werd een negatieve correlatie gevonden tussen de aanwezigheid van deze 'motivationele' symptomen enerzijds

en de score op de Verbal Fluency Test anderzijds. Ook met deze studie wordt het verband tussen cognitieve (executieve) functies en affectieve (motivationele) stoornissen bevestigd. Daarnaast lijkt het om een tamelijk specifiek verband te gaan, want met andere (niet-frontale) neuropsychologische testen werd geen relatie gevonden en de 'mood' symptomen vertoonden geen verband met de Verbal Fluency Test, noch met andere neuropsychologische testen.

De beide laatste hoofdstukken gaan over symptoomprofielen van depressie bij ouderen in de algemene bevolking. In ***hoofdstuk 6*** werd onderzocht in hoeverre het symptoomprofiel verschillend is in groepen depressieve ouderen met verschillende somatische risicofactoren. Uit de AMSTEL studie werden die ouderen met depressieve verschijnselen geselecteerd die een verhoogd risico hadden op vasculair, degeneratief of inflammatoir gebied. Vervolgens onderzochten we in hoeverre de symptomatologie per groep verschillend was. Zoals uit eerder onderzoek al bekend was, werd ook in deze studie voor alledrie de groepen een verhoogd risico op het ontwikkelen van een depressieve stoornis (DSM-diagnose) gevonden. Daarnaast werd op symptoom- en symptoomclusterniveau gevonden dat de 'motivationele' symptomen van depressie (psychomotore remming, interesse- en energieverlies) een sterkere associatie met zowel de vasculaire als degeneratieve groep vertoonden, terwijl de 'stemmings' symptomen (somberheid, ontstemming en suïcidaliteit) evenals de 'melancholische' symptomen (slapeloosheid, gebrek aan eetlust en gewichtsvermindering) een sterker verband met de inflammatoire groep hadden. Uit deze studie komt naar voren dat specifieke depressieve symptomatologie bij ouderen een indicatie kan zijn voor onderliggende, somatische/organische factoren.

Hoofdstuk 7 beschrijft een onderzoek naar het symptoomprofiel bij depressieve ouderen met vasculaire risicofactoren. Uitgangspunt bij deze studie was de 'vasculaire depressie' hypothese van Alexopoulos en Krishnan (beide 1997). Deze veronderstelt een specifiek subsyndroom van de depressie (meestal, maar niet uitsluitend bij ouderen), welke veroorzaakt wordt door atherosclerotische veranderingen van de hersenen. Hierbij staan psychomotore remming en anhedonie op de voorgrond, terwijl schuldgevoelens en suïcidaliteit minder voorkomen. In twee grote bevolkingsstudies, de AMSTEL en ERGO studie, werden deze specifieke symptoomprofielen echter niet teruggevonden. In zowel de AMSTEL als de ERGO studie werd bij depressieve ouderen met vasculaire risicofactoren vaker moeheid gevonden. In de AMSTEL studie had deze groep ook meer last van gebrek aan eetlust, in vergelijking met depressieve ouderen zonder deze vasculaire risicofactoren. In de AMSTEL studie werden deze symptomen overigens ook meer gezien bij alle ouderen met vasculaire risicofactoren, dus ongeacht de aanwezigheid van een volledig depressief syndroom.

CONCLUSIE

Hoofdstuk 8 geeft op basis van de bevindingen die in dit proefschrift zijn gemeld antwoorden op de vragen die bij aanvang zijn gesteld. Methodologische en conceptuele problemen van de studies uit dit proefschrift worden besproken. Er wordt ingegaan op de zin en onzin van symptoomprofielen, problemen rond de 'gouden standaard' en op de verschillende niveaus waarop naar een probleem als 'post-stroke' of 'vasculaire depressie' gekeken kan worden. Tot slot wordt het belang van de hier beschreven studies genoemd en wordt een voorstel gedaan voor verder onderzoek.

Summary

INTRODUCTION

This thesis is focused on the clinical presentation of depression in subjects with cerebrovascular disease, either patients with post-stroke depression (PSD), depression in subjects with vascular riskfactors like hypertension or diabetes, or with vascular lesions on MRI- or CT-scan. ***Chapter 1*** provides background information on the topic, on depressive disorder in general and more specifically on depression in the elderly and in relation with cerebrovascular disorders in general. Next, the combination of these two major general health problems, depression and cerebrovascular disease, is discussed. Post-stroke depression and 'vascular depression' are two important concepts that are commonly used in research. I discuss both concepts and summerize previous research on these topics. Important methodological problems that are encountered in these studies on subjects with depressive disorder in combination with vascular disease of the brain are explained. Next, I discuss the following aspects: Which definitions are used for depression? What is the temporal relationship between the depressive symptoms and the cerebrovascular lesions? Which groups are studied and what factors, other than neurobiological factors, can play a role in the development of depression in the elderly with concomitant cerebrovascular disease? I end up with the following questions that provide the basis for this thesis:

- What is the diagnostic value of the HAM-D for subjects who suffered from stroke and can this instrument be used for the purpose of screening and diagnosis of depression in these patients?
- Is there a distinct clinical symptom profile of depression for patients who suffer from severe vascular brain disease?
- Are the affective and cognitive sequelae of vascular brain damage interrelated?
- Can "vascular depression" be recognised as a distinct entity in the general population based on clinical depressive symptoms?

THE STUDIES

To answer the above-mentioned questions, I have used data of the following studies in this thesis:

The ***Dutch Vascular factors in Dementia Study*** concerns a study on patients who were admitted to a specialized, neurological university ward of the Erasmus Medical Center in Rotterdam, The Netherlands. Patients had to be 55 years or older and to have had a TIA with neurological signs on examination, a cerebral infarction, or intracerebral hemorrhage. The main purpose of this study was to gain insight in the influence of a broad spectrum of vascular factors on other risk factors, properties of the stroke itself and the occurrence of post-stroke dementia.

The ***Depression in Dementia Study*** concerns a longitudinal study that was carried out by the department of Psychiatry of the University Medical Center "St. Radboud" in Nijmegen, The Netherlands. Data collection took place from between 1990 – 1994. The purpose of this study was to prospectively investigate the connection between dementia and other psychiatric disorders, especially depression. In this study, 91 residents of a nursery home with dementia and 110 without were followed during 12 months. During this period 3 detailed examinations of psychogeriatric status were carried out, with special regard to symptoms and signs of dementia and depression and with neuropsychological tests. The study was funded by the JANIVO foundation.

The ***Amsterdam Study of the Elderly (AMSTEL)*** is a large population-based study that was carried out between 1990 – 1994. A total of 4051 subjects participated in a community dwelling study on mental health problems in the elderly. Trained interviewers examined them during home visits. The purpose of this study was to collect information on psychiatric symptoms, demographic and medical status, previous history and family history. It was carried out by the department of psychiatry of the Free University of Amsterdam, The Netherlands, embedded in the research program of the EMGO-institute. It was financially supported by the S.G.O. program (Stimulering Gezondheidszorg Onderzoek) of the ministry of VWS (health, welfare and sports). This ended in 1994 and since then the study was financed by the Nationaal Fonds Geestelijke Volksgezondheid and N.W.O.

The ***Rotterdam Study***, in the Netherlands also known as ERGO, is also a large, prospective population-based cohort study. It started in 1990 and at this moment the fourth follow-up round is carried out. In this thesis, data from the third round are used. In this study, all subjects of 55 years old and over out of the suburb Ommoord, Rotterdam, The Netherlands were involved. The main objective of the Rotterdam Study is to investigate the prevalence and incidence of and risk factors for chronic diseases in the elderly. Among the chronic diseases of interest are cardiovascular and neurological diseases. The study is carried out by the department of Epidemiology and Biostatistics of the Erasmus University Medical Center Rotterdam, The Netherlands. It was financially supported by the Research Institute of Diseases in the Elderly (RIDE, ZonMW). Additional funding for the depression study was given by Numico Research BV and for the atherosclerosis study by an extra gift by NOW, grant 904-61-091.

RESEARCH QUESTIONS

In ***Chapter 2*** I describe a study on the validity of the Hamilton Depression Rating Scale (HAMD) in subjects who suffered from a stroke. In everyday practice this rating scale is often used in subjects with a depressive disorder. It is constructed to be used in these patients for the purpose of measuring the severity of depressive symptoms and to monitor therapeutic effects of medication. In various studies on the prevalence of post-stroke depression the HAMD also frequently is used as a diagnostic tool. Actually, this is not permitted, because no reliable data are at hand on the psychometric properties on the subject of construct validity of this scale in this group of patients.

Data of the HAMD and thorough psychiatric examination were available from three different studies on subjects with various neurological disorders (stroke, Parkinson's disease and Alzheimer's disease). By means of ROC-curves cut-off scores for optimal sensitivity and specificity in the three disorders could be established. We found that the validity of the HAMD was good for all three patient groups, although for each group different, disease-specific cut-off scores should be used. As a diagnostic tool for depressive disorder in stroke patients, the optimal HAMD cut-off score was 10-11 points.

In ***chapter 3*** a study on phenomenology of depression in subjects with a stroke and concomitant cognitive disturbances (vascular dementia) is described. We included 78 subjects from the Dutch Vascular Factors in Dementia study in a subsequent psychiatric diagnostic interview. The majority of these subjects (N=54) fulfilled the NINDS-AIREN criteria for 'vascular dementia'. Detailed study of affective symptoms was done with help of the Schedule for Affective Disorders and Schizophrenia (SADS). This allowed us not only to establish a DSM-classification of major and minor depression, but also to study the prevalence and correlations of individual symptoms and various symptom-clusters. Using factor-analysis we found three different factors of depression. The first we called the 'mood' factor (mood in a strict sense) and this factor consisted of the symptoms sadness, dysphoria, ruminations, negative and suicidal thoughts and social withdrawal. The second factor was called the 'motivation' factor and consisted of psychomotor changes, anergia and a sad appearance. The third was called the 'vegetative' factor and consisted of anorexia and loss of weight. A few symptoms were not specific for one of these three factors and were therefore excluded from further analysis, namely insomnia, anhedonia and anxiety. All three selected factors had a strong correlation with the DSM-diagnosis "major depression". This is not surprising, because all three can be considered sub-syndromes of the full, major depressive syndrome. The motivation factor also had a strong correlation with the diagnosis of vascular dementia, whereas both the mood and the vegetative factor did not show such a correlation. The subsequent discriminant-analysis showed that motivational symptoms were indeed more frequent in the total group of

subjects with stroke (and additional dementia) in both depressed and non-depressed subjects. Therefore these symptoms show lower discriminant power than the symptoms of the 'mood' factor.

In ***chapter 4***, I provide an additional analysis of the study population of chapter 3. We assumed that the overlap between depression and dementia in this studygroup would foremost be determined by the motivational symptoms of depression. It is a subsyndrome of depression that has a remarkable resemblance to the frontal-subcortical symptoms of dementia or other neuro-degenerative disorders. We studied the correlation of the motivational symptoms of depression on one hand and the results on cognitive tests on frontal-subcortical functioning on the other. In this study, 54 subjects with post-stroke (vascular) dementia were included, in all of whom a careful diagnostic procedure was performed regarding cognitive as well as affective state. It concerned a group of subjects with moderate/severe dementia and mean scores on MMSE of 19.8 points (SD 5.0). Of this group 21 subjects (39%) fulfilled criteria of major depression according to DSM-IV. Although a comprehensive set of neuropsychological tests was presented to all subjects, a large proportion of them could not complete all tests because of severity of the cognitive problems. The only test that eventually could be applied to all subjects was the Verbal Fluency Test (VFT). This test is described as an important measure of frontal functioning, especially for the so-called 'executive functions'. In our study group we found a negative correlation between the score on the VFT and the motivational symptoms of depression. This means that subjects with a high score on the VFT (an indication of 'good' executive functioning) show less often motivational symptoms than subjects with low scores on the VFT. This supports our hypothesis that these frontal-subcortical, executive functions are implicated in the motivational symptoms of depression.

In ***chapter 5***, I address again the question on the interrelationship of affective and cognitive symptoms in subjects with mild cognitive impairment. In this study, 60 subjects with dementia from the Nijmegen study on depression in dementia were involved. DSM-III-R criteria of depression were divided into mood and motivation symptoms. A striking finding was that 77% of the depressive features in this group were actually motivational symptoms, mostly not in the context of a full depressive disorder. In addition, we found a negative correlation between the presence of these motivational symptoms on the one hand and the score on the Verbal Fluency Test (VFT) on the other, similar as described in chapter 4. Therefore, this study confirmed a relationship between cognitive (executive) function and affective (motivational) disorder, also since with other (non-frontal) cognitive tests no such a relationship was found for the 'motivational' symptoms and the 'mood' symptoms were neither related with the VFT nor with any other neuropsychological test.

The last two chapters focus on symptom profiles of depression in the elderly in the general population. ***Chapter 6*** describes our study on symptom profiles in groups of depressed elderly subjects with various somatic risk-indicators. From the AMSTEL study we selected those subjects with an increased risk of vascular, degenerative or inflammatory disease. Next, we investigated the depressive symptoms and we looked for differences in the profiles. From earlier studies it is known that all three somatic groups share an increased risk for developing depression. This was confirmed in our study. On the symptom and symptom cluster level, we found that the 'motivational' symptoms of depression (psychomotor changes, loss of interest and loss of energy) were associated with both the vascular and the degenerative group, whereas the 'mood' symptoms (sadness, dysphoria and suicidal thoughts) as well as the 'melancholic' symptoms (insomnia, anorexia and loss of weight) showed an association with the inflammatory group. From this study we conclude that the depressive symptom profile in the elderly could be an indication of the underlying somatic/organic disease.

Chapter 7 describes a study on the symptom profile of depressed elderly with vascular risk-factors. The starting point of this study was the 'vascular depression' hypothesis of Alexopoulos en Krishnan (both 1997). This hypothesis presumes a specific subsyndrome of depression (mostly in, but not restricted to the elderly) that is brought about by atherosclerotic changes of the brain. This syndrome has prominent psychomotor changes and anhedonia as major symptoms, whereas guilt feelings and suicidal ideation are less evident. In two large population-based studies, the AMSTEL and the Rotterdam Study, this specific symptom profile could not be found. In the AMSTEL as well as the Rotterdam study we found lassitude as the most prominent symptom in depressed elderly with vascular risk factors. In the AMSTEL study this group also showed anorexia more often compared with depressed elderly without vascular risk factors. However, in the AMSTEL study these symptoms were more frequent in all subjects with vascular risk factors, regardless of de presence of a complete depressive disorder.

CONCLUSION

In ***Chapter 8*** I summarize the findings of this thesis and discuss methodological and conceptual aspects. The usefulness of the presented symptom profiles, problems with the 'golden standard' of depression and the various levels at which the clinical problem of 'post stroke depression' and 'vascular depression' can be studied are discussed. Finally, I discuss the clinical relevance of the findings in this thesis and make suggestions for further research.

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Curriculum Vitae

Paul Naarding werd op 7 april 1966 geboren in Apeldoorn. In 1984 behaalde hij zijn VWO diploma aan de Koninklijke Scholengemeenschap te Apeldoorn. Datzelfde jaar startte hij met de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam, welke in 1990 werd afgerond met het artsendiploma. Vervolgens werkte hij als AGNIO 1 jaar op de afdeling Psychiatrie, 1 jaar op de afdeling Neurologie en een half jaar binnen de Medisch-Psychiatrische en Psychologische Dienst, allen van het Dijkzigt-ziekenhuis te Rotterdam.

In 1993 startte hij met de basis-opleiding tot psychiater op de afdeling Psychiatrie van het Academisch Ziekenhuis "Dijkzigt" te Rotterdam (opleider: Prof. Dr. W.J. Schudel). De stage Sociale Psychiatrie werd gedaan bij de Riagg Rijnmond Noord-West (Opleider: Dr. M.J.A.M. Coopmans). Als keuze-stage werd gekozen voor de Ouderenpsychiatrie en deze werd ingevuld bij de afdeling ouderen van het toenmalige Psychiatrisch Spectrum Gelderland Oost (PSGO, tegenwoordig GGNet), te Warnsveld (Stage begeleider: Drs. W.M.H. de Ruijter). Nadat in 1997 de registratie als psychiater een feit was, begon hij als afdelingspsychiater op de Geriatrische Afdeling van het Psychiatrisch Ziekenhuis (GAPZ) van het toenmalige Psychiatrisch Ziekenhuis Amsterdam (PZA, tegenwoordig Mentrum). Vervolgens maakte hij in 1999 de overstap naar de afdeling Psychiatrie van het Academisch Ziekenhuis "St. Radboud" te Nijmegen. Daar werkte hij op de polikliniek. Gelijktijdig had hij een deeltijdaanstelling bij Spatie te Apeldoorn en gaf hij daar mede gestalte aan een deeltijdbehandeling voor ouderen. Vanaf 2001 ging hij voltijds bij Spatie werken; het eerste jaar binnen cluster Ouderen, op de deeltijdbehandeling in combinatie met de polikliniek, vanaf 2002 tot op heden binnen het cluster Acute Psychiatrie, op de opname-afdeling volwassenen. Hij is mede-oprichter en voorzitter van de Medische Staf van Spatie. Vanaf 1 januari 2006 zal hij als A-opleider in dienst treden van Mediant, Centrum voor GGZ Oost- en Midden-Twente.

Paul Naarding woont in Apeldoorn, samen met Eveline en hun vier kinderen, Iris, Thijs, Koen en Nina.

List of publications

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1. Koudstaal PJ, van Gijn J, Naarding P, de Kluyver E, Pop GA, Staal A. 'Atypical TIAs' may herald cardiac rather than cerebral events. *Clin Neurol Neurosurg* 1991;93: 107-14.
2. van Kooten F, Hoogerbrugge N, Naarding P, Koudstaal PJ. Hyperglycemia in the acute phase of stroke is not caused by stress. *Stroke* 1993;24:1129-32.
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5. Naarding P, van den Broek WW, Koudstaal PJ. Cerebrovasculaire laesies en depressie. T*ijdschr Gerontol Geriatr* 1997;28:254-9.
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7. Naarding, P., Leentjens, A. F. G., van Kooten, F., and Verheij, F. R. J. Disease specific properties of the Hamilton Rating Scale for Depression (HAMD) in patients with stroke, Alzheimer's Dementia and Parkinson's Disease. *J Neuropsychiatry Clin Neurosci* 2002;14:329-34.
8. Naarding, P. and Verkes, R. J. Een patiënte met een maniforme ontremming na gebruik van een afslankmiddel. *Tijdschr Psychiatr* 2002;44:281-5.
9. Naarding, P., van den Broek, W. W., Wielaert, S., and van Harskamp, F. Aprosodia in major depressed patients. *J Neurolinguistics* 2003;16:37-41.
10. Naarding, P., de Koning, I., van Kooten, F., Dippel, D. W. J., Janzing, J. G. E., van der Mast, R.C. and Koudstaal, P. J. Depression in vascular dementia. *Int J Geriatr Psychiatr* 2003;18(4):325-30.
11. Naarding P, Janzing JGE. The neuropsychiatric manifestations of Huntington's Disease. *Current Opinion in Psychiatry* 2003;16(3):337-340.
12. Van Nijen AB, Naarding P. Reactie op 'Elektroconvulsietherapie als dwangbehandeling'. Ingezonden brief. Tijdschr Psychiatr 2003;45:461-3.
13. Gaasbeek D, Naarding P, Stor T, Kremer HPH. Drug-induced hyperthermia in Huntington's Disease. *J Neurology* 2004; 251: 454-7.
14. Hengeveld F, Naarding P. 'Recidiverende suicidepogers: hulp blijven aanbieden'. Ingezonden brief. NTvG 2005;148:2623.
15. Janzing JGE, Naarding P, Eling PATM. Depressive symptom quality and neuropsychological performance in dementia. *Int J Geriatr Psychiatry* 2005;20(5): 479-84.

16. Janzing JGE, Naarding P, Eling PATM. Depressive symptoms predict slow cognitive decline in mild dementia. *Dement Geriatr Cognit Disord* 2005; 20:77-81.
17. Arts, NJM, Naarding P. Neuropsychiatrische aspecten van de ziekte van Huntington. *Patient Care Neuropsychiatrie & Gedragsneurologie* 2005; 4:157-65.
18. Naarding P, Schoevers RA, Janzing JGE, Jonker C, Koudstaal PJ and Beekman ATF. A study on symptom profiles of late-life depression of vascular, degenerative or inflammatory origin. *J Affect Disord*, 2005;88:155-62.

BOOK CHAPTERS

1. Naarding P, Moleman P. Stemmingsstabilisatoren. In: Moleman P, ed. *Praktische psychofarmacologie*, 3e herziene druk. Houten/Diegem: Bohn Stafleu Van Loghum 1998: 140-209.
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3. Naarding P. Antidepressiva bij ouderen. In: Depressie bij ouderen. Verslag van symposium Leo Cahn stichting, 2001.
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SUBMITTED

1. Naarding P, de Koning I, van Kooten F, Janzing JGE, Beekman ATF, and Koudstaal PJ. Post stroke depression and dementia: frontosubcortical dysfunction as missing link?
2. Naarding P, Tiemeier H, Breteler M, Schoevers RA, Jonker C, Koudstaal PJ and Beekman ATF. Clinically defined vascular depression in the general population.