# The Neuropsychology of Acute Stroke

## Characterisation & Prognostic Implications

Neuropsychologische gevolgen in het vroege stadium na een beroerte
(met een samenvatting in het Nederlands)

Proefschrift

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door

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geboren op 31 oktober 1977, te Roeselare (België)

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## Brain explorer its for you

*Fragment by Tommy McHugh, who suffered a stroke in 2001.*
*Published in: Lythgoe MFX et al. (2005). Neurology, 64, 397-398.*

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*Voor mijn ouders*

# General Introduction

# Chapter 1

## Cognitive Impairment early after Stroke

### Aetiology & Diagnosis

## STROKE

### STROKE EPIDEMIOLOGY

Stroke is the third major cause of death and the leading cause of functional disability in Western countries. The incidence rate of stroke in the Netherlands is estimated at 170 to 190 in 100,000 inhabitants per year. This incidence will increase due to ageing of the population and epidemiological transitions (Hollander et al., 2003). About 120,000 to 140,000 stroke survivors are living in the Netherlands at this moment (Van Oers, 2002).

An ischaemic stroke or cerebral infarct occurs in 80% of all strokes, and is caused by an occlusion of a blood vessel in the neck or in the brain. The other less common type of stroke is a haemorrhagic stroke (20%), which is caused by rupture of a blood vessel resulting in the infiltration of blood into the surrounding tissue, either inside the brain tissue (intracerebral haemorrhage: 15%) or in the subarachnoid space surrounding the brain (subarachnoid haemorrhage: 5%). Most stroke trials, including our own, only report on patients with ischaemic infarction and intracerebral haemorrhage.

### RISK FACTORS AND TREATMENT

Numerous risk factors are associated with stroke, such as increasing age, male sex, black or Hispanic race/ethnicity, family history of stroke, hypertension, ischaemic heart disease, diabetes mellitus, hyperlipidaemia, atrial fibrillation, drug abuse, smoking, excessive alcohol consumption, physical inactivity, obesity, and hyperhomocysteinemia (Goldstein et al., 2001). The best approach to reduce the prevalence of stroke is a rapid control of those risk factors that are modifiable.

Stroke is not only a preventable but also a treatable disease. Since the first licence in the USA in 1996, a growing amount of research has been devoted to the effects of 'thrombolytic' intervention. This intervention is aimed at restoring cerebral blood flow before major ischaemic brain damage has occurred, and has been shown to exert a beneficial effect on clinical outcome (The NINDS rt-PA Stroke Study Group, 1995; Hacke et al., 1995). However, as the treatment is only safe and licensed within the first three hours post-stroke (Hacke et al., 2004), a revolution in neurologic services is needed with an emphasis on immediate care. At present, only about 10-20% of the potentially eligible patients in The Netherlands are receiving the treatment. Public education is essential in order to learn to recognise a stroke as such and to seek immediate care.

### Clinical manifestations

To date, the overall mortality rate from first-ever stroke in The Netherlands is still about 12% for ischaemic stroke and 33% for intracerebral haemorrhage in the first month, and corresponding one year case fatality rates are 24% and 63% (Hollander et al., 2003). Stroke survivors typically demonstrate a wide range of symptoms. Among the most prominent symptoms are motor deficits, sensory disturbances, aphasia, or hemianopia (Bogousslavsky & Caplan, 2001). These symptoms are clearly invalidating for the patient and have received a lot of attention in the literature and in clinical practice. Fewer studies have focused on the behavioural, cognitive, and emotional manifestations after stroke and these disorders are often overlooked in clinical practice (Bogousslavsky, 2003). Frequently occurring symptoms are personality changes (Stone et al., 2004) and neuropsychiatric disorders, such as post-stroke depression, anxiety disorders, or apathy (Bogousslavsky & Caplan, 2001). In addition, neuropsychological disorders, such as amnesia, executive dysfunction or unilateral neglect are common clinical manifestations after stroke and may be the single or dominant presenting features (Ferro, 2001). Although the brain is capable of reorganisation and significant cognitive recovery may occur in the first months post-stroke, a lot of patients do not show improvement at all or even deteriorate in the long term (Hochstenbach, Den Otter, & Mulder, 2003), resulting in post-stroke dementia (Rasquin et al., 2004). Our knowledge about the early cognitive manifestations, the course of recovery, the medical and neuro-imaging correlates, and the treatment of cognitive disorders is only beginning to emerge. In this thesis, I will focus on these issues in patients with a first symptomatic stroke.

## Acute Cognitive Disorders after Stroke

### Aetiology

In the early phase of stroke a cognitive disorder is usually related to direct local effects of the lesion, indicating that the afflicted brain area is an essential component in a network subserving that specific cognitive function. In case of ischaemic stroke, these local effects are related to the core area of the infarct and the ischaemic penumbra zone surrounding the infarct, whereas an intracerebral haemorrhage usually causes symptoms by exerting pressure on the surrounding brain tissue (Ferro, 2001).

In both types of stroke indirect effects may also play a role in causing cognitive impairment, such as (i) 'diaschisis' in which the lesion "cuts off" neural input to a remote area of the brain, causing dysfunction of that remote area (Ferro, 2001), (ii)

'hypoperfusion' in which neural dysfunction is caused by a decreased cerebral blood flow in case of stenosis or occlusion of one or more cerebropetal arteries (Hillis et al., 2004; Hillis et al., 2002), or (iii) neuronal metabolic abnormalities throughout the whole brain beyond the effects of the stroke lesion (Van Zandvoort, Van der Grond, Kappelle, & De Haan, 2005).

Finally, aspecific factors, such as fatigue, emotional distress, or pain may play an important role in exacerbating cognitive impairment in the early phase of stroke. The role of pre-existent vascular risk factors, such as diabetes mellitus, hypertension, or transient ischaemic attacks (TIAs) with respect to cognitive impairment in the early phase of stroke is presently unclear, but these factors have been shown to be related to long-term cognitive impairment after stroke (Gorelick, 1997).

### PREVALENCE AND CRITERIA FOR COGNITIVE IMPAIRMENT

The reported prevalence of cognitive deficits within the first month after stroke ranges widely from 10-82% (Rasquin et al., 2004), depending primarily on the criteria used to define cognitive impairment and on the selected patient population. Most studies on the relation between stroke and cognitive impairment have reported on 'vascular dementia' or post-stroke dementia in general. The concept of vascular dementia has recently been abandoned by most researchers because of the inconsistent criteria used to define vascular dementia (Pohjasvaara, Mantyla, Ylikoski, Kaste, & Erkinjuntti, 2000), and because the level of cognitive impairment required for a diagnosis of dementia prevents an early identification of patients with less severe but seriously invalidating cognitive disturbances (Roman, 2004).

Subsequently, a range of concepts which include milder forms of cognitive impairment have been developed over the past few years, such as 'vascular cognitive impairment' (VCI) (Bowler & Hachinski, 1995), 'mild cognitive impairment' (MCI) (Petersen et al., 1999), 'cognitive impairment no dementia' (CIND) (Graham et al., 1997), or 'vascular cognitive disorder' (VCD) (Sachdev, 1999). Although these concepts are preferable to that of vascular dementia, they still attempt to capture a very diverse phenomenon under one header, resulting in poor prognostic value and confusion in the literature. Moreover, these concepts tell us nothing about the nature of the underlying cognitive disorder and the specific disabilities that might arise from these deficits. Nevertheless, early diagnosis of specific cognitive deficits such as amnesia or executive dysfunction could be of great importance for determining an appropriate discharge destination and in particular for guiding rehabilitation. Also, interventions aimed at restoring specific cognitive functions could start off in an earlier stage, as studies in both animals (Biernaskie, Chernenko, & Corbett, 2004) and

humans (Paolucci et al., 2000) have shown that the brain displays a heightened sensitivity to rehabilitation early after the stroke as compared to later stages. Moreover, when after the hospital period the vast majority of survivors are discharged home, they are often ignorant of the existence and possible consequences of cognitive disorders, whereas an early identification and information provision might facilitate the patients' and caregivers' insight.

### The present study

Most clinicians consider fatigue, disorientation, overall malaise, or a fluctuating level of functioning in the early stage too prohibitive for proper neuropsychological assessment. Nevertheless, a recent publication from our group showed that an early neuropsychological examination was feasible in 85% of patients with a first-ever stroke (Van Zandvoort, Kessels, Nys, De Haan, & Kappelle, in press). This pilot study encouraged us to embark on a longitudinal study in a large cohort of patients with a first symptomatic stroke admitted to stroke units of three hospitals in the Netherlands (University Medical Centre Utrecht, Tweesteden Hospital Tilburg, and St. Elisabeth Hospital Tilburg) between December 2001 and July 2004. The patient cohort was studied within the first three weeks following stroke onset. In addition to a neuropsychological examination covering multiple cognitive domains, we collected demographic data, lesion characteristics, clinical factors at admission, and we recorded pre-existent vascular risk factors. The follow-up examination was administered after a minimum of six months and a maximum of ten months, in which we examined cognitive outcome, functional outcome, emotional outcome, and quality of life. A demographically matched healthy control group was also examined with the same time interval between baseline and follow-up assessment to control for practice effects and statistical artefacts.

## Aims and Thesis Outline

### Cognitive deficits after stroke: phenomenology and prognostic implications

The first aim of this thesis is to report on the phenomenology and prognostic implications of neuropsychological disorders in the early phase of stroke *(Chapters 2-5)*.

In *Chapter 2*, we examine the prevalence and nature of domain-specific cognitive disorders in the first three weeks after stroke, and we evaluate clinical associates of cognitive impairment in the early phase post-stroke. In *Chapter 3*, we report on the sensitivity and specificity of the Mini-Mental State Examination (MMSE) (Folstein,

Folstein, & McHugh, 1975), which is currently the mainstream of cognitive screening measures both in clinical practice and in scientific research. The MMSE was originally developed to screen for dementia in psychiatric populations, and has never been validated as an instrument to detect cognitive impairment in an acute stroke population. In *Chapter 4*, we focus on the relative contribution and prognostic value of acute cognitive disorders with respect to cognitive and functional outcome after six to ten months beyond that of other well-known medical and demographic predictors. *Chapter 5* studies the prevalence and nature of domain-specific cognitive recovery within the first months after stroke. Moreover, clinical determinants that predict recovery in these distinct cognitive functions are evaluated.

### The association between cognitive and emotional deficits after stroke

Secondly, this thesis addresses the association between cognitive impairment and depressive pathology after stroke *(Chapters 6-7)*. The mechanism by which stroke is associated with depression remains controversial with two opposing views. Some suggest that there is direct biological mechanism related to the location of the lesion. This view has been most strongly propagated by Robinson and his research group, who were the first to describe a relation between post-stroke depression and the location of the lesion (Robinson, Kubos, Starr, Rao, & Price, 1984). Others suggest a more indirect psychological mechanism according to which acute stressors associated with stroke are considered the primary cause of depression (e.g. Gainotti, Azzoni, & Marra, 1999). Related to this discussion is an ongoing debate regarding the direction of causality between cognitive impairment and depression after stroke. Recently, a third view has been proposed which states that not only stroke but chronic cerebrovascular risk factors in general predispose to or cause depression (Alexopoulos, 2003).

*Chapter 6* focuses on the relation between cognitive impairment and depressive symptoms early after stroke, and we examine lesion characteristics associated with depressive symptoms. In *Chapter 7*, the prognostic value of acute cognitive impairment with respect to depressive symptoms and quality of life after six months is examined, in addition to medical and demographic variables.

### Neurological treatment effects on cognition

In addition to studying neuropsychological impairment and the accompanying prognostic implications, the evaluation of cognitive functions can also serve to study the effects of different neurological treatment regimes. Thrombolytic treatment with intravenous recombinant plasminogen activator (rt-PA) is thought to result in an early

recanalisation of occluded arteries and in a subsequent reduction of lesion volume (The NINDS rt-PA Stroke Study Group, 2000). It has been shown that patients who receive thrombolytic treatment within the first three hours after stroke demonstrate a more favourable clinical outcome after three months compared to patients treated with placebo (Hacke et al., 1995). Until now, the effect of thrombolytic treatment on long-term cognitive outcome remains unknown. In the third part of this thesis *(Chapter 8)*, we examine the effect of thrombolytic treatment on long-term cognitive and functional outcome in patients with a first symptomatic ischaemic stroke.

### Uncommon cognitive disorders in acute stroke

The cognitive manifestations in the early phase of stroke are in general more severe than in later stages, as they reflect the dysfunction of a whole network. In contrast, some subtle manifestations and dissociations can only be detected if looked for in the first days after stroke onset (Ferro, 2001). Apart from the clinical merit, the neuropsychological assessment that we have developed allows for the early identification of patients with such uncommon disorders.

In the fourth part of this thesis *(Chapters 9-10),* two detailed neuropsychological case studies are reported. The first case study reports on the recovery course of a stroke patient (LW) who suffered from bilateral thalamic damage resulting in severe spontaneous confabulation, global amnesia, and executive dysfunction in the early phase of stroke *(Chapter 9)*. The second patient (RZ) suffered from a bilateral occipital infarction, resulting in hemianopia and complex visual hallucinations in the early phase of stroke. In this case report we study the neural correlates of these hallucinations by means of functional neuro-imaging *(Chapter 10)*. These case studies demonstrate the scientific and hypothesis-generating relevance of studying cognitive functioning in the early phase of stroke.

### Conclusions

*Chapter 11* includes a general discussion of the results presented in this thesis and suggestions for clinical practice and future research. Methodological strengths and weaknesses of our study are discussed. Finally, a summary of the findings is provided.

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# Cognitive deficits after stroke

## Phenomenology & Prognostic Implications

# Chapter 2

## Cognitive Disorders in Acute Stroke

### Prevalence and Clinical Determinants

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**ABSTRACT**

*Objective* Although cognitive impairment early after stroke is a powerful predictor of long-term functional dependence and dementia, little is known about the characteristics and determinants of cognitive dysfunction in acute stroke. The aim of the present study was to compare the prevalence and nature of acute cognitive disorders between patients with cortical, subcortical, and infratentorial stroke, and to examine clinical determinants of acute cognitive impairment.

*Methods* We administered an extensive neuropsychological examination covering 7 distinct cognitive domains to 190 consecutive patients within three weeks after a first symptomatic stroke. In addition, we assembled lesion characteristics from CT or MRI, clinical factors at admission, demographic characteristics, and pre-existent vascular risk factors. Multivariate logistic regression adjusted for age, sex, and education was performed to examine independent determinants of early cognitive impairment.

*Results* In the early phase of stroke, 74% of patients with a cortical stroke, 46% of patients with subcortical stroke, and 43% with infratentorial stroke demonstrated cognitive impairment in at least one cognitive domain. Disorders in executive functioning (39%) and visual perception and construction (38%) were the most common. The prevalence and severity of deficits in executive functioning, language, verbal memory, and abstract reasoning was more pronounced following left compared to right cortical stroke (all $p<0.05$). Primary intracerebral haemorrhage (O.R.=5.6; 95%CI=1.2-25.4) and cortical involvement of the stroke (O.R.=3.6; 95%CI=1.3-9.9) were independent determinants of early cognitive impairment, whereas premorbid moderate alcohol consumption showed a trend towards protection (O.R.=0.4; 95%CI=0.1-1.1).

*Conclusion* Cognitive impairment is common in the first weeks after stroke, with executive and perceptual disorders being the most common. Patients with cortical involvement of the lesion and with haemorrhagic stroke are particularly at risk for demonstrating cognitive impairment in the early phase of stroke, whereas premorbid moderate alcohol consumption may exert a protective effect.

## INTRODUCTION

Neuropsychological disorders are common manifestations in the early phase of stroke and may be the single or dominant presenting features. Acute cognitive disorders are related to the lesion itself, but often also to hypoperfusion and functional deactivation (diaschisis) of more distant areas in the brain. In addition, both ischaemic and haemorrhagic stroke may cause symptoms by exerting pressure on the surrounding brain tissue and by causing a deviation of nearby or more distant brain structures (Ferro, 2001). Finally, aspecific factors, such as fatigue, emotional distress, or pain may play an important role in exacerbating cognitive impairment in the early phase of stroke (Lezak, Howieson, & Loring, 2004).

Acute cognitive disorders are powerful predictors of long-term cognitive impairment (Nys et al., 2005), dementia (Rasquin, Lodder et al., 2004), dependence in basic and more complex activities of daily life (Nys et al., 2005), the presence of depressive symptoms (Nys et al., submitted), and a reduced quality of life (Nys et al., submitted). Therefore, the modification of risk factors of early cognitive impairment may result in a more favourable outcome. However, clinical determinants of cognitive impairment in the early phase of stroke are largely unknown. To our knowledge, only one study has examined associates of cognitive impairment in the early phase of stroke (Rasquin, Verhey, Van Oostenbrugge, Lousberg, & Lodder, 2004). In this study, a close association with age, education, and 'territorial' (i.e. non-lacunar supratentorial) infarcts was demonstrated. To date, the relation between early post-stroke cognitive impairment and pre-existent lesions, vascular risk factors or other potentially important factors at admission, such as hyperglycaemia or fever, has never been examined. These factors may be important as they are related to dementia and poor cognitive outcome in elderly patients without a history of stroke (e.g. Biessels, Van der Heide, Kamal, Bleys, & Gispen, 2002; Papademetriou, 2005; Vermeer et al., 2003).

In addition, little is known about the prevalence and nature of acute cognitive deficits following subcortical and infratentorial stroke, although a few lesion studies in selective stroke samples have shown that these stroke types may cause a considerable amount of cognitive impairment (Hillis et al., 2002; Hillis, Wityk, Barker, Ulatowski, & Jacobs, 2003). Another aspect that has remained elusive concerns the hemispheric asymmetry of complex cognitive functions such as executive functioning and abstract reasoning in patients with cortical and subcortical stroke. It is particularly interesting to look at these issues before neuronal and/or cognitive compensation has taken place. Whereas recovery of function after a stroke is in part attributable to events in the first few days (e.g. reabsorption of perilesional oedema or tissue reperfusion),

consistent reorganisation and recovery after a stroke usually take a few weeks or even months (Rossini & Dal Forno, 2004).

The aim of the present study is to examine in detail the phenomenology and clinical determinants of cognitive impairment in the first three weeks after stroke, and to compare the nature of specific cognitive deficits between patients with left and right cortical and subcortical lesions.

## METHODS

### PATIENTS

The study population consisted of 228 consecutive patients with first-ever symptomatic stroke admitted to a stroke unit in one of three hospitals in the Netherlands (University Medical Centre Utrecht, Tweesteden Hospital Tilburg, and St.-Elisabeth Hospital Tilburg) between December 2001 and January 2003. Patients were eligible for inclusion if they had had either an ischaemic stroke or a primary intracerebral haemorrhage provided that they had no neurological or psychiatric history. The diagnosis of stroke was based on the presence of an acute focal deficit, confirmed by an associated lesion on CT or MRI. Patients with a normal scan underwent a second scan within the first week post-stroke. Patients with a history of drug or alcohol abuse, pre-existent dependence in activities of daily living, pre-existent cognitive decline (as defined by a score of 3.6 or higher on the short Informant Questionnaire on Cognitive Decline in the Elderly – IQCODE Dutch Version) (De Jonghe, Schmand, Ooms, & Ribbe, 1997), or patients older than 85 years were excluded. This procedure resulted in a study population of 190 patients with acute stroke (Figure 1). This population has been reported previously (Nys et al., 2005).

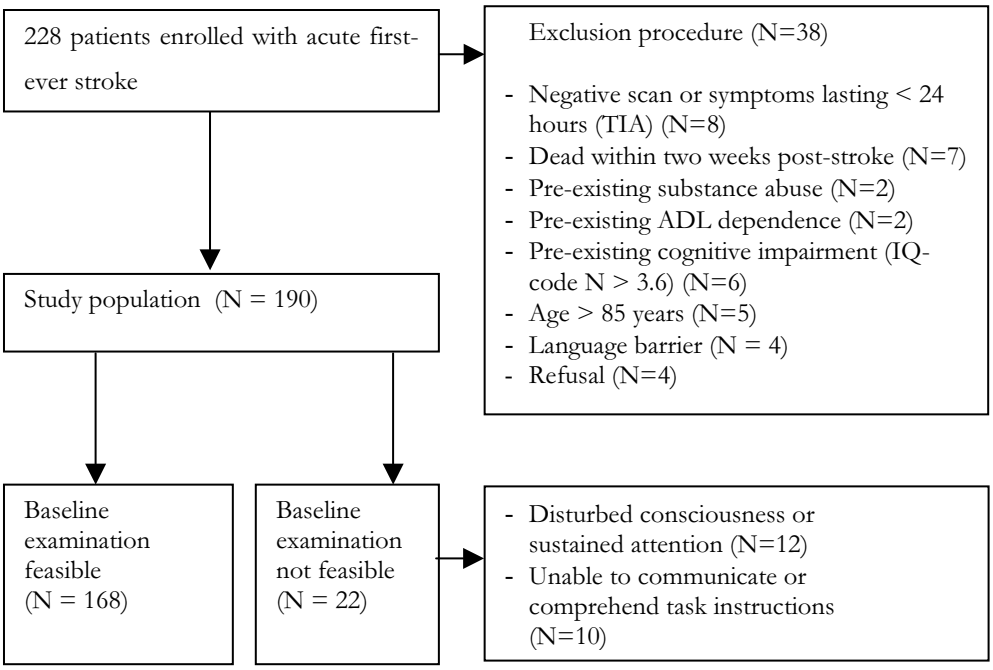


FIGURE 1. Characterisation of patient cohort.

### CONTROLS

A control group was assembled as a reference sample for the neuropsychological examination, and consisted of 90 subjects living in the community. The controls were either spouses or family of patients, or volunteers who came to our attention through advertising in newspapers or by word of mouth. The same exclusion procedure was adopted for the control subjects as for the stroke patients, which resulted in the inclusion of 75 healthy subjects. The control subjects were comparable to the patients with respect to age (62.3 ± 16.8 vs. 62.8 ± 14.1), education (4.5 ± 2.4 vs. 4.3 ± 1.5), sex (60% females vs. 51% females), and hand preference (right hand preference 83.1% vs. 85.7%) (all $p>0.05$).

### NEUROPSYCHOLOGICAL EXAMINATION

The neuropsychological examination was performed within the first three weeks after stroke, and was split up in two sessions (on two successive days) if the patient was too tired or if a medical examination was required at the time of testing. The examination covered seven major cognitive domains (Lezak et al., 2004): (1) *Abstract reasoning* was assessed with the Raven Advanced Progressive Matrices (short form: 12 items) for

spatial reasoning, and Similarities (WAIS-III) for verbal reasoning; (2) *Verbal memory* was measured with the Digit Span (WAIS-III) [total score forward and backward] for verbal working memory, and with the Rey Auditory Verbal Learning Test [total words direct recall, unexpected delayed recall after 30 minutes, and recognition] for verbal short- and long-term memory; (3) *Executive functioning* was assessed with the Brixton Spatial Anticipation Test for non-verbal concept formation and flexibility, the Visual Elevator [accuracy score and reaction time] (Test of Everyday Attention) for verbal cognitive flexibility (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994), and Letter Fluency [N and A: 1 minute]; (4) *Visual perception and construction* was assessed with the Judgment of Line Orientation [short form: 15 items] for visuo-spatial orientation, the Test of Facial Recognition [short form: 13 items] for matching and recognition of faces, and the Rey-Osterrieth Complex Figure–copy for visual construction; (5) *Visual memory* was measured with the Corsi Block Span forward for visual working memory and the Rey-Osterrieth Complex Figure-delay (unexpected delayed recall after 30 minutes) for non-verbal long-term memory; (6) *Language* was assessed with the Token Test [short form: 21 items] for language comprehension and the Boston Naming Test [short form: 30 items] for language production; (7) *Spatial attention* was measured with the Star Cancellation (Behavioural Inattention Test) in order to detect unilateral neglect.

The neuropsychological examination in the early phase of stroke was considered feasible if patients were able to perform at least 10 of the 15 tasks, which allowed evaluation of the majority of the cognitive domains. Based on this criterion, the examination could not be performed in 22 patients (12%) due to disorders in consciousness or sustained attention, or because of very severe aphasia (Figure 1). Patients who were able to reach this criterion but who were unable to perform one or more tasks were given the minimum score on the task(s) they could not perform, as it is impossible to differentiate between patients who might be able to perform a task but who are hampered by another deficit (e.g. Broca's aphasia) and patients who are unable to perform the task because of an underlying deficit in that domain. The procedure of administering multiple neuropsychological tasks within one cognitive domain allowed us to transform raw test scores of patients on individual tasks into compound z-scores based on the means and standard deviations of the control group. Subsequently, we averaged z-scores of tasks belonging to the same cognitive domain (Nys et al., 2005). The internal consistency (Cronbach's alfa) of the distinct cognitive domains varied between 0.70 and 1.0, indicating an acceptable level of reliability (Nunnaly, 1978). Cut-off scores for cognitive impairment within each domain were determined by a performance that differed from the control mean at the 0.05 level of

significance (z-score < -1.65) (Clark-Carter, 1997). This value is also associated with the fifth percentile level of performance (Lezak et al., 2004).

### POTENTIAL DETERMINANTS OF COGNITIVE IMPAIRMENT

We recorded the patients' age (years), sex, and level of education (using a Dutch classification system ranging from 1: did not finish primary school to 7: university degree). Education was dichotomised as either low (0-4) or high (5-7) (Nys et al., 2005).

Furthermore, we recorded the following vascular risk factors: previously diagnosed and treated diabetes mellitus, hypertension, hypercholesterolaemia, transient ischaemic attack (TIA), smoking during the last five years, and alcohol consumption of more than 2 units per day.

In addition, we recorded factors associated with the patients' medical status on admission, i.e. body temperature > 38º C in the first week during hospital stay, admission glucose level (mmol/L), total serum cholesterol level at admission (mmol/L), and systolic and diastolic blood pressure (mmHg).

An experienced stroke neurologist (HBvdW) who was blind to the neuropsychological data evaluated the patients' stroke type from CT or MRI, in addition to the location of the lesion (classified according to lesion side and lesion site, i.e. cortical involvement of the lesion, exclusive subcortical involvement of the lesion, and infratentorial involvement). The volume of the lesion was calculated using Leica Q500 MCP image analysis software by manual tracing of the lesion on each slice showing the infarct or haemorrhage, followed by multiplying lesion area by slice thickness in all slices showing the lesion. This method has been shown to have a high inter-rater reliability and is described in detail elsewhere (Van der Worp et al., 2001).

The presence of pre-existent brain pathology was scored using straightforward dichotomous ratings. Silent infarcts were classified as present when an infarct was found in the brain without the description by the patient, family, or medical record of a prior stroke episode (Nys et al., 2005). Cerebral atrophy was classified as present when a generalised dilatation of cortical sulci was found, with or without associated ventricular enlargement) (Nys et al., 2005). White matter lesions were scored as present if patients obtained a score > 0 on the 'Van Swieten scale') (Van Swieten, Hijdra, Koudstaal, & Van Gijn, 1990).

### STATISTICAL ANALYSES

First, the prevalence and severity of cognitive deficits was compared between patients with left and right stroke by means of $\chi^2$ analyses and Student t-tests. Next,

multivariate logistic regression analysis adjusted for age, sex, and education was performed to examine independent determinants of cognitive impairment in the early phase of stroke. The variables with a univariate association at $p \leq 0.1$ were entered into logistic regression. The Hosmer-Lemeshow goodness-of-fit statistic (Hosmer & Lemeshow, 1989) is reported to determine if the model provides a good fit for the data. Models are well calibrated and fit the data if the goodness-of-fit statistic is large ($p > 0.05$).

## RESULTS

### COGNITIVE MANIFESTATIONS IN THE EARLY PHASE OF STROKE

Of the 190 included patients, 168 patients (88%) could be examined within the first three weeks post-stroke. The examination was administered at a mean of 7.9 ± 4.2 days since stroke onset. On the whole, 89 patients (55%) demonstrated cognitive impairment ranging from an isolated impairment to impairment in multiple cognitive domains. In total, 39.1% showed a deficit in executive functioning, 38.1% in visual perception and construction, 31.3% demonstrated unilateral neglect, 25.6% demonstrated a deficit in abstract reasoning, 25.6% in verbal memory, 25.6% in language, and 22.0% in visual memory. Figure 2 shows the number of cognitive impairments subdivided according to ischaemic or haemorrhagic stroke. These groups did not significantly differ in age, education, sex, or lesion volume (all $p > 0.05$).

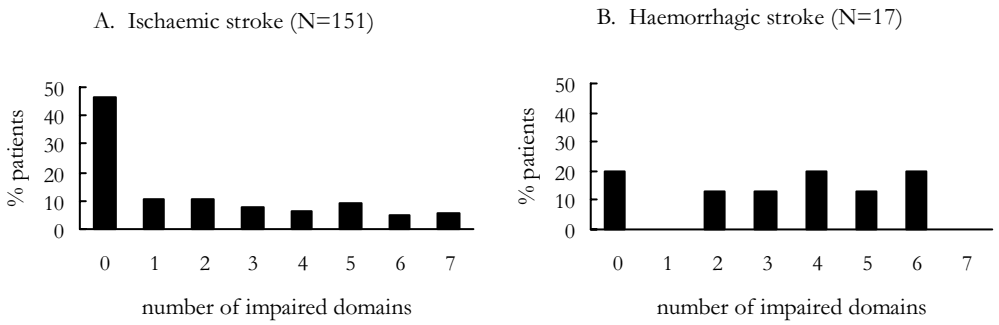


FIGURE 2. Severity of cognitive impairment in patients with acute ischaemic stroke (A) or acute intracerebral haemorrhage (B).

Cognitive impairment in at least one cognitive domain was found in 74% of patients with a cortical stroke, in 46% of patients with subcortical stroke, and in 43% of patients with infratentorial stroke. The frequency and severity of distinct cognitive deficits classified according to lesion side and location is shown in Table 1.

TABLE 1. Frequency and severity of cognitive deficits according to stroke location.

| | Prevalence | | | Severity‡ | | |
|---|---|---|---|---|---|---|
| | Left | Right | p | Left | Right | p |
| Cortical stroke | n=28 | n=35 | | n=28 | n=35 | |
| Abstract reasoning | 67.9% | 25.0% | .001* | -1.6 ± 1.4 | -0.9 ± 0.9 | 0.02* |
| Verbal memory | 64.3% | 28.1% | .005* | -2.6 ± 1.9 | -1.1 ± 1.0 | 0.001* |
| Executive function | 71.4% | 43.8% | .03* | -2.1 ± 1.4 | -1.4 ± 1.1 | 0.03* |
| Visual memory | 28.6% | 31.3% | .82 | -1.0 ± 1.4 | -1.1 ± 1.3 | 0.80 |
| Perception/construction | 50.0% | 53.1% | .81 | -2.1 ± 2.5 | -2.3 ± 2.4 | 0.69 |
| Language | 60.7% | 25.0% | .005* | -3.6 ± 3.2 | -0.8 ± 1.4 | 0.001* |
| Unilateral neglect | 28.6% | 51.6% | .07 | -6.9 ± 14.7 | -13.1 ± 18.3 | 0.16 |
| Subcortical stroke | n=35 | n=29 | | n=35 | n=29 | |
| Abstract reasoning | 20.0% | 13.8% | 0.36 | -0.6 ± 1.3 | -0.5 ± 1.0 | 0.94 |
| Verbal memory | 17.1% | 10.3% | 0.44 | -1.1 ± 1.4 | -0.8 ± 0.8 | 0.21 |
| Executive function | 28.6% | 27.6% | 0.93 | -0.9 ± 1.3 | -0.9 ± 1.1 | 0.86 |
| Visual memory | 22.9% | 17.2% | 0.58 | -0.7 ± 1.2 | -0.7 ± 1.2 | 0.88 |
| Perception/construction | 28.6% | 24.1% | 0.69 | -1.3 ± 2.4 | -1.2 ± 1.7 | 0.84 |
| Language | 25.7% | 10.3% | 0.12 | -0.8 ± 1.9 | -0.4 ± 0.9 | 0.24 |
| Unilateral neglect | 17.6% | 36.0% | 0.11 | -3.4 ± 12.0 | -4.7 ± 10.5 | 0.68 |
| Infratentorial stroke | n=22 | | | n=22 | | |
| Abstract reasoning | 13.6% | | | -0.5 ± 1.1 | | |
| Verbal memory | 18.2% | | | -0.6 ± 0.8 | | |
| Executive function | 27.3% | | | -0.7 ± 1.0 | | |
| Visual memory | 13.6% | | | 0.0 ± 1.1 | | |
| Perception/construction | 40.9% | | | -1.0 ± 1.7 | | |
| Language | 22.7% | | | -0.4 ± 1.2 | | |
| Unilateral neglect | 14.3% | | | -2.7 ± 10.6 | | |

Based on N=149 due to small amounts of missing data. ‡ Severity: values indicate mean domain scores ± standard deviations. Lower scores indicate worse performance. * $p<0.05$.

Demographic and clinical characteristics that are univariately associated with the presence of acute cognitive impairment after stroke are shown in Table 2.

TABLE 2. Factors associated with cognitive impairment in acute stroke (N=168).

| | Cognitively intact (N=79 - 47%) | Cognitively impaired (N=89 - 53%) | p-value |
|---|---|---|---|
| Demographics | | | |
| Age, years | 60.0 ± 14.3 | 65.2 ± 13.5 | 0.02* |
| Sex, female | 40.5 | 59.6 | 0.01* |
| High education‡ | 58.2 | 28.6 | 0.001* |
| Vascular risk factors | | | |
| Hypercholesterolaemia | 19.0 | 11.5 | 0.18 |
| TIA(s) | 12.7 | 17.0 | 0.43 |
| Diabetes mellitus | 11.4 | 15.9 | 0.40 |
| Hypertension | 40.5 | 44.3 | 0.62 |
| Smoking during last 5 years | 40.5 | 38.6 | 0.81 |
| Alcohol > 2 units /day | 26.6 | 11.4 | 0.01* |
| Clinical factors at admission | | | |
| Serum glucose, mmol/L | 7.2 ± 3.7 | 7.9 ± 3.1 | 0.24 |
| Serum cholesterol, mmol/L | 5.8 ± 1.4 | 5.7 ± 1.1 | 0.63 |
| Diastolic blood pressure, mmHg | 93.9 ± 16.7 | 91.4 ± 17.3 | 0.34 |
| Systolic blood pressure, mmHg | 171.1 ± 33.0 | 163.5 ± 29.0 | 0.11 |
| Temperature > 38º | 7.6 | 21.6 | 0.01* |
| Stroke-related characteristics | | | |
| Stroke type | | | 0.01* |
| Infarct | 96.2 | 84.3 | |
| Haemorrhage | 3.8 | 15.7 | |
| Lesion location | | | 0.54 |
| Left hemisphere | 39.1 | 45.7 | |
| Right hemisphere | 40.6 | 40.7 | |
| Left and right hemisphere | 2.9 | 1.2 | |
| Brain stem | 11.6 | 4.9 | |
| Cerebellum | 5.8 | 7.4 | |
| Lesion site | | | 0.002* |
| Cortical | 26.1 | 54.3 | |
| Subcortical | 56.5 | 33.3 | |
| Infratentorial | 17.4 | 12.3 | |
| Volume, $cm^3$ | 9.3 ± 16.5 | 27.3 ± 38.3 | 0.001* |
| Pre-existent pathology | | | |
| Cerebral atrophy | 11.3 | 14.5 | 0.56 |
| Silent infarct(s) | 21.1 | 15.9 | 0.40 |
| White matter lesions | 20.3 | 25.8 | 0.39 |

‡High education = 5 (high school education) to 7 (university degree). Values are within-group percentages or means ± standard deviations.

Multivariate logistic regression analyses adjusted for age, sex, and education indicated that cortical involvement of the lesion (O.R.=3.6; 95%CI=1.3-9.9) and haemorrhagic stroke (O.R.=5.6; 95%CI=1.2-25.4) were independent risk factors of cognitive impairment in the early phase after stroke, whereas moderate alcohol consumption (O.R.=0.4; 95%CI=0.1-1.1) showed a protective trend. Nagelkerke R-square of this model was 0.42 and the goodness-of-fit of the model was sufficient (p=0.7).

## Discussion

The present study is the first in which a broad range of cognitive domains was carefully assessed in a large population of patients in a very early phase after stroke (mean interval eight days post-stroke). Our findings show that patients with a lesion involving the cortex demonstrated the largest prevalence of cognitive deficits, particularly those with a left cortical stroke. On the whole, a disorder in executive functioning, abstract reasoning, verbal memory, and/or language was present in 60% to 70% of these patients. It should be noted that our neuropsychological assessment of executive functioning and abstract reasoning included both verbal and nonverbal neuropsychological tasks. Our findings with respect to the higher prevalence of executive dysfunction following left hemisphere damage replicate those of a recent study in patients three months following ischaemic stroke (Vataja et al., 2003). Although both the left (e.g. Cabeza & Nyberg, 2000; Goldstein, Obrzut, John, Ledakis, & Armstrong, 2004; Johnson-Frey, Newman-Norlund, & Grafton, 2004) and the right hemisphere (e.g. Stuss & Levine, 2002) have been shown to be implicated in complex cognitive functioning such as abstract reasoning and executive functioning, an intact language comprehension is presumably crucial in order to display an unimpaired performance on tasks assessing these functions, as has been shown recently (Baldo et al., 2005) and in some older studies (De Renzi, Faglioni, Savoiardo, & Vignolo, 1966; Gainotti, D'Erme, Villa, & Caltagirone, 1986). In a similar vein, it has been shown that the disruption of inner speech in healthy controls resulted in an impaired executive functioning and spatial reasoning (Baldo et al., 2005). Taken together, the close relation between language and complex cognitive processes may explain the higher prevalence of these disorders in patients with left compared to right cortical stroke.

Traditionally, executive dysfunction has been associated with frontal lobe damage. However, both lesion studies (e.g. Vataja et al., 2003) and functional imaging studies (e.g. Baker et al., 1996; Fassbender et al., 2004) have shown that the executive functions are associated with a widely distributed network of cortical areas (such as parietal, cingulate, premotor, occipital, and temporal cortex), subcortical areas (the

basal ganglia and thalamus), and infratentorial areas (cerebellum and pontine areas). Given the variable distribution of lesions in our patients it is therefore not surprising that executive dysfunction was found to be the most common cognitive deficit after stroke in the present study.

Another frequent deficit was a disorder in visual perception and construction. Again, functional imaging studies during visual perception typically reveal bilateral activation in a widespread network including frontal, parietal, temporal, and occipital areas, the basal ganglia, the thalamus, and the cerebellum (Ganis, Thompson, & Kosslyn, 2004). The prevalence of deficits in visual perception/ construction and visual memory was equal in patients with left and right cortical damage in our study. Similarly, other higher-level visual abilities, such as visuo-spatial abilities or spatial memory, have been shown to be sensitive both to left and right hemisphere damage, although the underlying processes specialised by each hemisphere might be different (e.g. Carlesimo, Fadda, & Caltagirone, 1993; Kessels, Kappelle, De Haan, & Postma, 2002; Mehta & Newcombe, 1991). Interestingly, our study shows that 40% of patients with infratentorial lesions demonstrated a deficit in visual perception and construction. Previous lesion studies have demonstrated visuo-spatial deficits associated with cerebellar damage (Malm et al., 1998; Molinari, Petrosini, Misciagna, & Leggio, 2004; Schmahmann & Sherman, 1997). The neural basis of these deficits remains unclear. Ascending cerebellar and brain stem projections to fronto-parietal areas and their feedback loops may be responsible for the infratentorial involvement in the processing of spatial information. Moreover, functional neuroimaging studies of the cerebellum have also demonstrated activation of the cerebellum in mental rotation (Tagaris et al., 1998), line bisection judgment (Fink et al., 2000), and other visuo-spatial skills such as visual imagery (Ganis et al., 2004).

The right hemisphere dominance in spatial attention is well known for decades, and one of the models explaining this asymmetry poses that the right hemisphere directs attention to both the ipsi- and contralateral hemispace, whereas the left hemisphere directs attention almost exclusively to the contralateral right hemispace (Mesulam, 1981). Similarly, lesion studies have convincingly shown that unilateral neglect is more frequent and severe following right hemisphere brain damage (Robertson & Marshall, 1993). Whereas our study shows a higher prevalence and severity of unilateral neglect following right hemisphere damage, this difference was not statistically significant. This might have to do with our inclusion of severely aphasic patients, who in some cases also showed severe unilateral neglect. Moreover, we examined our population early after stroke. A previous study has shown that neglect was equally common in the acute stage (3 days) after right and left hemispheric stroke (72% vs. 62%) (Stone et al., 1991). However, three months later neglect had

dramatically decreased in left hemispheric stroke patients (33%), whereas it remained frequently present after right hemispheric stroke (75%) (Stone, Patel, Greenwood, & Halligan, 1992).

In our study, cognitive impairment in the early phase of stroke was present in about one in two patients with a subcortical stroke. Whereas cognitive impairment in these patients may be a direct effect of the subcortical lesion itself (indicating that the afflicted subcortical area is an essential component of that specific cognitive network), it may also result from a functional disconnection and/ or hypoperfusion of cortical structures (Hillis et al., 2002). It has been demonstrated that improvement in perfusion of the overlying cortex in the first days following stroke onset parallels recovery of cognitive deficits caused by subcortical stroke (Hillis et al., 2002; Vallar et al., 1988). The lack of hemispheric asymmetry with respect to cognitive deficits in patients with subcortical stroke is intriguing. Whereas a substantial number of studies has reported hemispheric functional asymmetry at the subcortical level in later stages of stroke (Annoni et al., 2003; Fimm et al., 2001), we could not demonstrate this difference in the early phase of stroke, perhaps in part due to a lack of statistical power.

Although there were no significant differences in lesion size or demographic characteristics between patients with ischaemic and haemorrhagic stroke, the latter had a six times greater frequency of acute cognitive impairment than the former. This is in line with previous studies performed at later stages post-stroke (Arboix et al., 2002; De Koning et al., 1998; Su et al., 2000). Of the patients with haemorrhagic stroke, 80% had a cognitive deficit in two or more domains, whereas isolated cognitive deficits did not occur in this patient group. The relatively worse cognitive outcome after haemorrhagic stroke may be due to widespread intracranial pressure effects, resulting in decreased levels of alertness and confusion (Arboix et al., 2002).

Patients with premorbid moderate alcohol consumption tended to show a reduced risk of developing cognitive impairment in the early phase of stroke. Previous studies also demonstrated a protective effect of moderate alcohol consumption against the development of dementia (Ruitenberg et al., 2002) or cognitive impairment (Stampfer, Kang, Chen, Cherry, & Grodstein, 2005) in non-stroke samples. Several mechanisms have been proposed to explain this effect, with one of the most plausible being the consistently lower rate of cardiovascular disease among moderate alcohol drinkers (Stampfer et al., 2005). However, in our study the protective effect of alcohol was independent of previous vascular risk factors, and all patients had had a stroke. The explanation therefore remains unknown.

In sum, our study demonstrates that one in two patients with first-ever stroke suffer from cognitive impairment in the early phase of stroke. The prevalence of

executive disorders and disorders in visual perception and construction was the most common. Patients with cortical involvement of the stroke and with primary intracerebral haemorrhage were particularly at risk for demonstrating cognitive impairment in the early phase of stroke, whereas premorbid moderate alcohol consumption may show a protective effect.

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# Chapter 3

## Restrictions of the Mini-Mental State Examination in Acute Stroke

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**ABSTRACT**

While the Mini-Mental State Examination (MMSE) was originally developed to screen for dementia and delirium, many neurologists use this measure as a screening instrument for 'cognitive impairment' in hospitalised stroke patients. However, the validity of the MMSE as such has never been evaluated in acute stroke. We administered the MMSE in addition to a neuropsychological examination covering six cognitive domains to 34 stroke patients (mean interval between stroke and examination, 6.5 ± 2.9 days) and 34 healthy controls. The area under the receiver operating characteristic curve (AUC) was calculated in addition to the sensitivity and specificity for various cut-off points on the MMSE.

Seventy percent of the patients were impaired in at least one cognitive domain. The accuracy of the MMSE in detecting cognitive impairment was no better than chance (AUC=0.67; p=0.13). No optimum MMSE cut-off value could be identified. The MMSE is particularly insensitive to impairments in abstract reasoning, executive functioning, and visual perception/ construction.

## INTRODUCTION

Cognitive disorders in the acute stage of stroke are common and are important independent predictors of adverse outcome in the long term (Nys et al., 2005). Therefore, a whole range of brief cognitive measures has been used to screen for cognitive impairment in patients with acute stroke. The Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) is currently the mainstay of screening instruments. This instrument was originally developed to screen for dementia and delirium in a psychiatric setting, and has been shown to have a good sensitivity and specificity as such (Folstein et al., 1975). Subsequently, the use of the MMSE has been extended and many studies now use it as a screening instrument for 'global cognitive impairment' (e.g. Narushima, Chan, Kosier, & Robinson, 2003; Patel, Coshall, Rudd, & Wolfe, 2003). However, the validity of the MMSE as a cognitive screening instrument has been questioned in both neurological and psychiatric patients (Faustman, Moses, & Csernansky, 1990; Grace et al., 1995). Moreover, there is no consensus in the cut-off values that are applied to discriminate between cognitively intact and impaired patients.

Blake and co-workers recently investigated the sensitivity and specificity of the MMSE as a screening tool for post-stroke cognitive impairment (Blake, McKinney, Treece, Lee, & Lincoln, 2002). They compared performance on the MMSE in the early stage of stroke with performance on a neuropsychological examination that was administered within three months of the screening assessment. The sensitivity of the MMSE when applying a cut-off value of <24 was found to be moderate (62%). However, given that there was a very large inter-individual variation in the test interval and that the degree of cognitive recovery is greatest in the first months post-stroke (Lezak, Howieson, & Loring, 2004), their methodology may have resulted in an overestimation of the sensitivity of the MMSE in initially impaired patients who had recovered by the time of the neuropsychological examination.

The aim of the present study was to evaluate the utility of the MMSE as a screening instrument for cognitive impairment in patients with acute stroke. The MMSE and a full neuropsychological examination covering six cognitive domains was administered within two weeks post-stroke, and the diagnostic sensitivity and specificity of the MMSE was examined. Moreover, we evaluated which cognitive deficits were most often disregarded by the MMSE.

## Methods

### Subjects

The patient population consisted of 38 consecutive acute stroke patients admitted to stroke units of two hospitals in the Netherlands (Tweesteden Hospital & St.-Elisabeth Hospital Tilburg). Eligible patients were patients with either ischaemic stroke or primary intracerebral haemorrhage. The diagnosis of stroke was based on the presence of both an acute focal deficit and an associated lesion on CT or MRI. Exclusion criteria for this study were a high degree of handicap (modified Rankin Scale > 4) (N=1), non-native speaker (N=1), and severe disturbances in communication and consciousness (N=1). One patient was blind (pre-existent impairment) and therefore was not included in this study. This resulted in a study population of 34 stroke patients.

A control group was assembled as a reference sample for the neuropsychological examination, consisting of 34 subjects living in the community. The controls were volunteers who came to our attention through advertising in newspapers or by word of mouth. Control subjects were carefully matched to the stroke patients with respect to age, education, sex and handedness (Table 1).

### Procedure

Basic demographic information was collected including age, sex, handedness, and level of education. Level of education was scored according to a Dutch classification system consisting of seven categories ranging from 1: primary school not finished, to 7: university degree obtained (Nys et al., 2005). Patient and control characteristics are presented in Table 1.

An experienced stroke neurologist classified ischaemic strokes according to the Oxford Community Stroke Project (OCSP) classification (Bamford, Sandercock, Dennis, Burn, & Warlow, 1991), which is a simple clinical scheme to subdivide acute strokes. Patients may be classified by using clinical criteria only, although we did have CT or MRI scans available to differentiate ischaemic and haemorrhagic stroke types. Subtypes of the OCSP are lacunar infarct/haemorrhage (LACI/LACH), partial anterior circulation infarct/haemorrhage (PACI/PACH), total anterior circulation infarct/haemorrhage (TACI/TACH), and posterior circulation infarct/haemorrhage (POCI/POCH). The side of the stroke lesion and history of stroke were also noted. The modified Rankin Scale was used to measure the patients' degree of handicap (Van Swieten, Koudstaal, Visser, Schouten, & Van Gijn, 1988). The scale consists of six grades, from 0 (no symptoms) to 5 (severe disability).

Within two weeks post-stroke, each patient underwent the MMSE and in the same session a detailed neuropsychological examination lasting 1.5 hours entailing the following cognitive domains (Lezak et al., 2004): (1) abstract reasoning [Raven Advanced Progressive Matrices (short form) and Similarities (WAIS-III)], (2) verbal memory [Rey Auditory Verbal Learning Test and Digit Span WAIS-III], (3) executive functioning [Letter fluency, the Brixton Spatial Anticipation Test, which is a measure of strategic switching and problem-solving that does not require a verbal response (Burgess & Shallice, 1997), and the Visual Elevator (Test of Everyday Attention) (Robertson et al., 1994) in which patients have to count up an down as they follow a series of visually presented floors in an elevator; this test assesses cognitive flexibility], (4) visual perception and construction [Judgement of Line Orientation (short form), Test of Facial Recognition (short form), Rey-Osterrieth Complex Figure–copy], (5) visual memory [Corsi Block Span and Rey Complex Figure Delay], and (6) language [Token Test (short form) and Boston Naming Test (short form)]. The short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE Dutch Version) (De Jonghe, Schmand, Ooms, & Ribbe, 1997) was administered as a measure of pre-existent cognitive functioning. This questionnaire is a homogenous rating scale, which asks an informant about changes in the patients' everyday cognitive function.

TABLE 1. Patient and control characteristics (N = 34 for each group).

| | Patients | Controls | p-value |
|---|---|---|---|
| Demographics | | | |
| Age, mean ± SD | 64.7 ± 11.5 | 65.7 ± 12.0 | 0.7 |
| Male sex, % | 41.2 | 41.2 | 1.0 |
| Education, median [range]* | 4 [1-7] | 4 [2-7] | 0.2 |
| Handedness, right, % | 88.2 | 85.3 | 0.5 |
| Degree of handicap | | | |
| Modified Rankin Scale, median [range] | 3 [1-4] | | |
| Pre-existent cognitive functioning | | | |
| IQ-code | 3.3 ± 0.4 | | |
| Oxford Community Stroke Project | | | |
| LACI | 21 | | |
| PACI | 5 | | |
| POCI | 6 | | |
| TACI | 1 | | |
| POCH | 1 | | |
| Recurrent stroke, n | 14 | | |
| Lesion side, n | | | |
| Right | 17 | | |
| Left | 17 | | |

* Education level is scored using 7 categories (1= not finished primary school; 7= university degree). Abbreviations: LACI=lacunar infarct; PACI=partial anterior circulation infarct; POCI=posterior circulation infarct; TACI=total anterior circulation infarct; POCH= posterior circulation haemorrhage.

### STATISTICAL ANALYSIS

Patients' neuropsychological test results were standardised into z-scores, based on the means and standard deviations of the control group. Next, we created cognitive domain scores by averaging z-scores of tasks belonging to the same cognitive domain. Cut-off scores for cognitive impairment within each domain were determined for a performance that differed from the control mean at the 0.05 level of statistical significance (z-score < -1.65) (Clark-Carter, 1997). Patients without a deficit in one of the cognitive domains were considered to be cognitively intact.

Pearson or Spearman correlation coefficients were calculated between the MMSE score and (1) age, (2) education level, and (3) IQ-code. The area under the receiver operating characteristic curve (AUC) was calculated for the MMSE in relation to the presence of overall cognitive impairment as assessed with the neuropsychological examination. The AUC can vary between 0.5 and 1. The ideal test has an AUC of 1,

meaning 100% sensitivity and specificity. The sensitivity and the specificity for various cut-off points of the MMSE were determined (sensitivity = true positives / true positives + false negatives; specificity = true negatives / true negatives + false positives). When evaluating the usefulness of a screening measure to identify those individuals with cognitive impairment, a good sensitivity (>80%) is required, while maintaining an acceptably low false positive rate (specificity>60%) (Blake et al., 2002).

## RESULTS

The mean interval between the stroke event and the neuropsychological examination was 6.5 ± 2.9 days [range 2-14]. Overall, 70% of patients were impaired in at least 1 cognitive domain as assessed with the neuropsychological examination. More specifically, 47% of patients demonstrated an impairment in abstract reasoning, 32% showed an impairment in executive functioning, 26% in language, 21% in visual perception and construction, 15% in verbal memory, and 12% in visual memory. The prevalence of patients with cognitive impairment according to the MMSE is shown in Table 2.

TABLE 2. Sensitivity and specificity of the MMSE. Percentage of patients classified as cognitively impaired according to the MMSE.

| MMSE cut-off | Sensitivity | Specificity | Prevalence of cognitive impairment according to MMSE |
|---|---|---|---|
| <23 | 30.4% | 100% | 23.5% |
| <24 | 34.8% | 70% | 35.3% |
| <25 | 56.5% | 60% | 52.9% |
| <26 | 69.6% | 40% | 67.6% |
| <27 | 95.7% | 40% | 85.3% |
| <28 | 100% | 40% | 88.2% |
| <29 | 100% | 30% | 91.2% |

Grey areas indicate acceptable sensitivity (> 80%) or specificity (> 60%).

The median score on the MMSE was 24 [range 14-30]. There was no significant correlation between the MMSE score and the age of patients ($r = -.14$, $p>0.05$), education level ($r = 0.28$, $p>0.05$), or pre-existent level of cognitive functioning (IQ-code) ($r = 0.02$, $p>0.05$).

When differentiating patients with cognitive impairment from cognitively intact patients, the MMSE had an AUC of 0.67 (standard error=0.11), indicating that the

MMSE performed statistically no better than chance (p=0.13). The sensitivity and specificity of the MMSE is presented in Table 2. No optimum cut-off scores yielding both a sensitivity greater than 80% and a specificity greater than 60% could be identified.

When applying a cut-off value of <24, which is a frequently used cut-off value for hospitalised patients, 11 of the 16 patients (69%) with reasoning disturbances in the early phase of stroke were misclassified as cognitively intact by the MMSE, as were 7 of the 11 patients (64%) with executive disorders, 4 of the 7 patients (57%) with visual perceptual impairments, 2 of the 4 patients (50%) with visual memory deficits, 4 of the 9 patients (44%) with language disorders, and 1 of the 5 patients (20%) with verbal memory disorders.

## DISCUSSION

The present study shows that the MMSE is an invalid screening tool to discriminate between cognitively intact and impaired patients with acute stroke. Before we interpret our findings, it should be noted that the majority of patients in our sample included patients with subcortical lacunar stroke. Nevertheless, 70% of this population demonstrated cognitive impairment, which may in part have been caused by a previous stroke, and our study shows the insensitivity of the MMSE to detect cognitive impairment as such. Our findings are in contrast with the good sensitivity and specificity that has been reported when the MMSE is used as a screening tool for dementia (Folstein et al., 1975). Prior studies have reported other limitations of the MMSE, such as insensitivity to right-hemisphere lesions (Dick et al., 1984; Grace et al., 1995), mild cognitive disturbances (Schwamm, Van Dyke, Kiernan, Merrin, & Mueller, 1987), and amnesia (Benedict & Brandt, 1992). While most studies adopt a cut-off value of <24 to indicate intact cognition in stroke patients, our findings show that the sensitivity of the MMSE is extremely poor when using this value (34.8%). Consequently, in a majority of cognitively disturbed patients, impairments may not be taken into account in planning both discharge destination and rehabilitation trajectory. Cognitive disorders that are most often disregarded by the MMSE in acute stroke patients are impairments in more complex cognitive functioning such as abstract reasoning and executive functioning, but also in visual perception and construction. Given that our findings also show that impairments in reasoning and executive functioning are the most frequent cognitive impairments in the early phase post-stroke, the MMSE should be interpreted with caution when used as a screening instrument for cognitive impairment in patients with acute stroke.

In an ongoing large-scale longitudinal study, we are examining the nature and prevalence of specific cognitive disorders in acute stroke patients and the recovery patterns associated with these cognitive disorders. This may elaborate our understanding in the nature of impairments in these patients and perhaps in the development of a stroke-specific cognitive screening instrument. Moreover, during the last couple of years several new screening instruments have been developed which incorporate items that assess executive functioning and reasoning, e.g. the CAMCOG (De Koning et al., 1998), and the seven minute screen (7MS) (Meulen et al., 2004). The sensitivity and specificity of these instruments remains to be determined in acute stroke, but it is likely that these measures are more appropriate than the MMSE in detecting post-stroke cognitive impairment.

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# Chapter 4

# The Prognostic Value of Domain-specific Cognitive Abilities in Acute First-ever Stroke

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**ABSTRACT**

*Objective* To evaluate the prognostic value of domain-specific cognitive abilities in acute stroke with respect to long-term cognitive and functional outcome in addition to neurological and demographic predictors.

*Methods* We evaluated 168 patients within the first three weeks after first-ever stroke. The prevalence of neuropsychological impairment was calculated vs. 75 matched healthy controls. We also recorded demographic data, vascular risk factors, lesion characteristics, and clinical factors at admission. Independent predictor variables associated with long-term cognitive impairment (assessed with a follow-up neuropsychological examination) and functional impairment (assessed with the modified Barthel Index and the Frenchay Activities Index) were identified with stepwise multiple logistic regression. Areas under receiver operator characteristic curves were used to compare the predictive value of three models, i.e. a standard medical model, a purely cognitive model, and a model consisting of both medical and cognitive predictors.

*Results* Thirty-one percent of patients showed long-term cognitive impairment. Basic and instrumental ADL disturbances remained present in 19% and 24 % of patients. Domain-specific cognitive functioning predicted cognitive and functional outcome better than any other variable. Moreover, the prediction of instrumental ADL functioning improved when cognitive predictors were added to the standard medical model ($p<0.05$). Impairments in abstract reasoning and executive functioning were independent predictors of long-term cognitive impairment. Neglect and perceptual disorders were more important in predicting long-term functional impairment.

*Conclusion* Domain-specific cognitive abilities in the early phase of stroke are excellent independent predictors of long-term cognitive and functional outcome.

## INTRODUCTION

Several factors have been identified as predictors for long-term disability and adverse outcome, such as initial stroke severity and lesion characteristics, functional status at admission with respect to activities of daily life (ADL), vascular risk factors, and demographic factors (Hankey, Jamrozik, Broadhurst, Forbes, & Anderson, 2002; Jorgensen et al., 1999; Miyai, Suzuki, Kang, & Volpe, 2000; Thijs et al., 2000; Weimar, Konig, Kraywinkel, Ziegler, & Diener, 2004). While cognitive disorders are among the most frequent and devastating early consequences of stroke (Ferro, 2001), only few studies have examined the prognostic importance of these acute disorders (Galski, Bruno, Zorowitz, & Walker, 1993; Paolucci et al., 1996). Moreover, most of these studies have used global cognitive screening measures in the early phase of stroke, although these measures demonstrate poor sensitivity in detecting cognitive impairment in stroke patients (Blake et al., 2002). Also, these global measures do not allow evaluation of cognitive performance in specific domains. Other studies on post-stroke cognitive impairment have focused on the prognostic value of isolated impairments such as unilateral neglect (Hillis et al., 2003; Kalra, Perez, Gupta, & Wittink, 1997), anosognosia (Appelros, Karlsson, Seiger, & Nydevik, 2002), aphasia (Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001), or apraxia (Pedersen et al., 2001). A detailed neuropsychological evaluation covering the whole cognitive spectrum in acute stroke has not been reported yet, probably because of uncertainty about the feasibility and reliability of such early testing (Lezak, Howieson, & Loring, 2004). Therefore, it is unknown whether certain types of domain-specific cognitive impairment are more disabling on the long term than others.

We sought (1) to investigate whether a detailed neuropsychological examination in the acute stage after stroke contributes to the prediction of long-term cognitive and functional outcome in addition to well-known medical predictors, and (2) to examine whether certain types of domain-specific cognitive impairment are more related to outcome than others.

## METHODS

### PATIENTS

The population consisted of 228 consecutive patients with first-ever symptomatic stroke admitted to stroke units of three hospitals in the Netherlands (University Medical Center Utrecht, Tweesteden Hospital Tilburg, and St.-Elisabeth Hospital Tilburg) between December 2001 and January 2003. Patients were eligible if they had

either ischaemic stroke or primary intracerebral haemorrhage. The diagnosis of stroke was based on the presence of both an acute focal deficit and an associated lesion on CT or MRI. Patients with a normal scan underwent a second scan within the first week post-stroke. Exclusion criteria were: (1) Pre-existing impairment or history that might influence cognitive or functional outcome, i.e. history of substance abuse, pre-existent dependence in activities of daily living, or pre-existent cognitive decline (as defined by a score of 3.6 or higher on the short Informant Questionnaire on Cognitive Decline in the Elderly – IQCODE Dutch Version) (De Jonghe, Schmand, Ooms, & Ribbe, 1997), (2) patients older than 85 years, and (3) patients who could not be examined within the first 21 days post-stroke due to severe disturbances in consciousness or inability to comprehend task instructions. This exclusion procedure resulted in a study population of 190 patients with acute stroke, of which 168 patients (88%) could be neuropsychologically examined.

Finally, patients who suffered a recurrent stroke or who developed comorbidity that might affect outcome (i.e. cancer, myocardial infarction, CABG, or psychiatric illnesses) between the first and the second examination were excluded from follow-up examination. Figure 1 presents a chart showing the number of patients who were in- and excluded from this study.

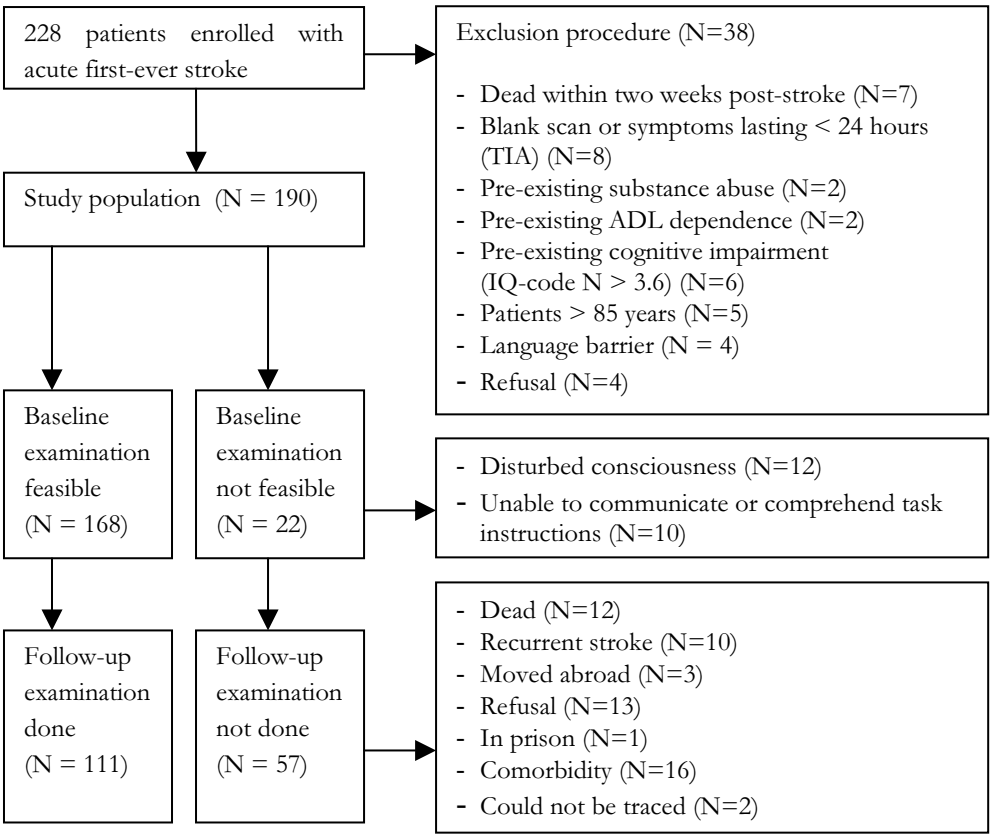


FIGURE 1. Characterisation of patient cohort at baseline and at follow-up.

### CONTROLS

A control group was assembled as a reference sample for the neuropsychological examination, consisting of 75 subjects living in the community. The controls were either spouses or family of patients, or volunteers who came to our attention through advertising in newspapers or by word of mouth. Control subjects were carefully matched to the stroke patients with respect to age, education, and sex. Moreover, they performed both examinations with the same time interval as the patients to control for potential practice effects.

### PREDICTOR VARIABLES

On admission, demographic factors, vascular risk factors, factors associated with medical status at admission, CT/MRI characteristics, and domain-specific cognitive abilities were obtained as candidate predictor variables. All except the continuous

predictor variables were dichotomised in order to reduce the number of variables and for clinical clarity. Demographic factors included age (years), sex, and level of education (scored according to a Dutch classification system consisting of 7 categories ranging from 1:did not finish primary school to 7:university degree, and dichotomised at the median). Vascular risk factors comprised previously diagnosed diabetes mellitus, hypertension, hypercholesterolaemia, transient ischaemic attack (TIA), smoking during the last five years, and alcohol consumption of more than 2 units per day. Factors associated with the patients' medical status on admission were body temperature > 38º C in the first week during hospital stay, admission glucose level, total serum cholesterol level at admission, systolic and diastolic blood pressure, stroke severity (assessed by means of the National Institutes of Health Stroke Scale (Brott et al., 1989), and categorised as severe if NIHSS > 7) (DeGraba, Hallenbeck, Pettigrew, Dutka, & Kelly, 1999), functional dependence (assessed by means of the modified Barthel Index [MBI] (Mahoney & Barthel, 1965), and categorised as present if MBI < 19) (Weimar et al., 2004) and weakness of either arm or leg (categorised as present if NIHSS items for either arm or leg > 1). An experienced stroke neurologist (HBvdW) who was blind to the clinical data evaluated the patients' stroke type (categorised as cerebral infarct or intracerebral haemorrhage) from CT or MRI, in addition to the location of the lesion (classified into three categories, that is involvement of left hemisphere, right hemisphere, and brain stem/cerebellum), the main affected territory of vascular blood supply (classified as anterior, middle, or posterior cerebral artery, or vertebrobasilar arteries), the presence of silent infarcts (classified as present when an infarct was found in the brain without the description by the patient, family, or medical record of a prior stroke episode) (Kase et al., 1998), the presence of cerebral atrophy (classified as present when a generalised dilatation of cortical sulci was found, with or without associated ventricular enlargement) (Kase et al., 1998), white matter lesions (scored as present if patients obtained a score > 0 on the 'Van Swieten scale') (Van Swieten, Hijdra, Koudstaal, & Van Gijn, 1990), and the volume of the lesion, calculated using Leica Q500 MCP image analysis software by manual tracing of the lesion on each slice showing the infarct or haemorrhage, followed by multiplying lesion area by slice thickness in all slices showing the lesion. This method has been shown to have a high inter-rater reliability and is described in detail elsewhere (Van der Worp et al., 2001).

A detailed cognitive examination was performed within three weeks post-stroke (mean time from onset to examination, 8.3 ± 4.5 days). An extended evaluation took place after a minimum of 6 and a maximum of 10 months post-stroke. Both the baseline and the follow-up examination covered seven major cognitive domains consisting of verbal and nonverbal neuropsychological tasks (tasks added to the

follow-up examination are italicised) (Lezak et al., 2004). Reasoning was assessed with the Raven Advanced Progressive Matrices (short form) and Similarities (WAIS-III). Verbal memory was measured by means of the Rey Auditory Verbal Learning Test, the Digit span (WAIS-III), and the *Wechsler Memory Scale – Story Recall A*. Executive functioning was assessed with the Brixton Spatial Anticipation Test, the Visual Elevator (Test of Everyday Attention) (Robertson et al., 1994), letter fluency, the *Stroop Colour Word test, Semantic Fluency, and the Zoo test (BADS)*. Visual perception and construction was assessed with the Judgment of Line Orientation (short form), the Test of Facial Recognition (short form), the Rey-Osterrieth Complex Figure–copy, and the *WAIS-III Block Patterns*. Visual memory was measured with the Corsi Block Span, the Rey-Osterrieth Complex Figure-delay, the *Wechsler Memory Scale-Visual Reproduction, and the Location Learning Task* (Bucks, Willison, & Byrne, 2000). Language was assessed with the Token Test (short form), the Boston Naming Test (short form), and the *Chapman Reading Task*. Finally, unilateral neglect was measured with the Star Cancellation (BIT), the NIHSS neglect item and the *Line Bisection Schenkenberg*.

The neuropsychological examination in the early phase of stroke was considered feasible if patients were able to perform at least 10 of the 15 tasks, which allowed evaluation of the majority of the cognitive domains. Patients who were able to reach this criterion but who were unable to perform one or more tasks were given the minimum score on the tasks they could not perform. In this way, both patients with aphasia and unilateral neglect could be included in our study. The procedure of administering multiple neuropsychological tasks within one cognitive domain allowed us to transform raw test scores of patients on individual tasks into compound z-scores based on the means and standard deviations of the control group on the first and second examination to control for potential practice effects. Subsequently, we averaged z-scores of tasks belonging to the same cognitive domain. Cut-off scores for cognitive impairment within each domain were determined by a performance that differed from the control mean at the 0.05 level of significance (z-score $< -1.65$) (Clark-Carter, 1997). This approach was used for both (acute and follow-up) neuropsychological examinations.

### OUTCOME MEASURES

Two distinct types of outcome were used in the present study, i.e. long-term cognitive outcome and functional outcome in terms of ADL.

Cognitive outcome was assessed with the abovementioned neuropsychological examination at follow-up and classified as 'cognitively intact' [defined as no

impairment on any of the cognitive domains] vs 'cognitively impaired' [defined as an impairment in at least one cognitive domain].

Functional outcome was assessed with two separate ADL measures, that is basic and instrumental ADL measures. Basic ADL instruments assess straightforward activities such as personal hygiene and dressing, whereas instrumental ADL instruments assess more complex ADL, such as grocery shopping, household management, and social activities. In this study, basic ADL was determined with the modified Barthel Index (MBI) (Mahoney & Barthel, 1965). A MBI value ≥ 19 was used as an indication of intact basic ADL function (Weimar et al., 2004). The Frenchay Activities Index (FAI) (Wade, Legh-Smith, & Langton Hewer, 1985) was used to assess instrumental ADL. In total, the scale comprises 15 individual activities summed to give an overall score ranging from 0 (inactive) to 45 (very active). Intact instrumental ADL function was defined as FAI ≥ 15 (Wilkinson et al., 1997).

All outcome measures were dichotomised in order to provide clear and interpretative information for both clinicians and patients. Outcomes were assessed blind to the predictor variables.

### Statistical analyses

First, to determine whether any selection bias occurred between patients who were re-examined at follow-up and those who were not, we performed Student t-tests for continuous data, Mann-Whitney U tests for ordinal data and $\chi^2$ analyses for categorical data on a range of baseline characteristics of patients.

Second, univariate analyses of potential predictor variables were undertaken for the three outcome measures. Those variables with a univariate association at $p \leq 0.1$ were considered for entry into forward stepwise multiple logistic regression analysis. Three multivariate prediction models were produced for each outcome measure. A standard 'medical' model was developed entering all variables associated with outcome in the univariate analyses, except for the early cognitive predictors. The cognitive model included only cognitive factors associated with outcome in the univariate analyses. The combined model included both medical and cognitive predictors. Receiver-operator characteristic (ROC) curves were used to compare the information content of the different models for all outcome measures (Hanley & McNeil, 1983). The larger the area under the ROC curve (AUC), the higher the information content of the model. The Hosmer-Lemeshow goodness-of-fit statistic was used to determine if the models provided a good fit for the data (Hosmer & Lemeshow, 1989). Models are well calibrated and fit the data if the goodness of fit statistic is large ($p > 0.05$).

## Results

### Clinical characteristics of patients not examined at follow-up

As shown in Figure 1, 111 of 168 (66%) patients were re-examined. The interval between the early examination and follow-up did not differ between controls (7.4 ± 1.3 months) and patients (7.4 ± 1.0 months). Patients who were not examined at follow-up were older, more impaired on the MBI at baseline, and experienced more deficits in executive functioning, visual memory, and visual perception and construction at baseline. The failure to be re-examined was also related to the presence of silent infarct(s) and white matter lesions, whereas no association with vascular risk factors or characteristics directly related to the stroke lesion could be demonstrated (Table 1).

TABLE 1. Comparison of characteristics between patients included and not included for follow-up.

| Baseline characteristics | Included (N=111) | Not included (N=57) |
|---|---|---|
| Demographics | | |
| Age, mean ± SD* | 60.1 ± 14.2 | 67.9 ± 12.5 |
| Education, median [range] | 4 [0-7] | 4 [2-7] |
| Sex, male | 54.1 | 40.4 |
| Stroke type | | |
| Infarct | 90.1 | 89.5 |
| Haemorrhage | 9.9 | 10.5 |
| Lesion location | | |
| Left hemisphere | 43.8 | 44.6 |
| Right hemisphere | 41.0 | 44.6 |
| Brain stem/cerebellum | 15.2 | 10.7 |
| Vascular supply area | | |
| Anterior | 3.0 | 6.1 |
| Middle | 66.0 | 57.1 |
| Posterior | 15.0 | 22.4 |
| Vertebrobasilar | 16.0 | 14.3 |
| Silent infarct(s)* | 13.7 | 27.5 |
| White matter lesions* | 15.3 | 38.6 |
| Cerebral atrophy | 10.7 | 17.6 |
| Stroke severity and functional status at baseline | | |
| NIHSS score, median [range] | 5 [0-18] | 5 [1-18] |
| MBI, median [range]* | 17 [1-20] | 15 [1-20] |
| Vascular risk factors | | |
| Hypertension | 40.0 | 47.4 |
| Diabetes mellitus | 10.9 | 19.3 |
| Hypercholesterolemia | 17.3 | 10.7 |
| Transient ischemic attack | 14.5 | 15.8 |
| Cognitive impairments at baseline | | |
| Abstract reasoning | 24.5 | 30.9 |
| language | 20.9 | 32.1 |
| Verbal memory | 20.9 | 32.1 |
| Visual memory* | 16.8 | 32.7 |
| Executive functioning* | 30.3 | 50.0 |
| Visual perception and construction* | 31.2 | 49.1 |
| Unilateral neglect | 10.9 | 14.0 |

Values are within-group percentages unless indicated otherwise. Some within-group percentages are based on incomplete samples due to small amounts of missing data. Analyses are chi-square analyses or Fisher exact tests (categorical data), Mann-Whitney U Tests (ordinal data) or t-tests (continuous data). *$p<0.05$. Abbreviations: NIHSS = National Institutes of Health Stroke Scale; MBI=modified Barthel Index.

### PREVALENCE OF ADVERSE OUTCOME ON THE LONG TERM

Of the included patients, 48.6% showed cognitive impairment(s) in the first three weeks post-stroke, whereas 30.6% of patients showed cognitive impairment at follow-up in at least one cognitive domain, indicating a decline in the number of patients with cognitive impairment ($p<0.001$). Remaining basic ADL disturbances were found in 18.7% of patients, whereas 24.3% demonstrated instrumental ADL disability. Associations between the three outcome measures are presented in Figure 2. 54.9% of patients demonstrated a complete recovery with respect to all outcome measures, whereas 10.8% of patients demonstrated an incomplete recovery with regard to all three outcome measures.

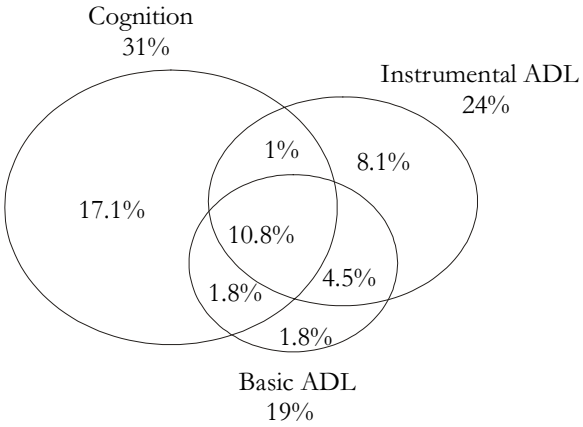


FIGURE 2. Association of outcome measures.

### DETERMINANTS OF COGNITIVE IMPAIRMENT ON THE LONG TERM

Univariate analyses showed that cognitive impairment on the long term was associated with older age, lower education, female sex, no regular alcohol consumption, lower MBI at baseline, body temperature > 38º C, glucose level at admission, large lesion volume, and impairments in all cognitive domains at baseline (all $p\leq0.1$) (Table 2). These predictor variables were introduced into multivariate stepwise logistic regression analysis to find independent predictors of long-term cognitive impairment. In the medical model, cognitive impairment was associated with a large lesion volume, female sex, and older age, whereas the cognitive model yielded two independent predictors, i.e. impairments in executive functioning and abstract reasoning (Table 3). In the combined model cognitive impairment on the long term was associated with

impairments in executive functioning and abstract reasoning, and female sex. Lesion volume and age dropped from this model because these variables failed to reach statistical significance. Patients with executive impairments at baseline nearly had 7-fold greater odds of being cognitively impaired six months later, whereas patients with early reasoning disturbances had 4-fold greater odds of obtaining an adverse cognitive outcome (Table 3). All three models demonstrated an acceptable fit by the Hosmer-Lemeshow test. The combined model yielded the largest AUC, followed by the cognitive model (Figure 3). However, the difference between the three models did not reach significance.

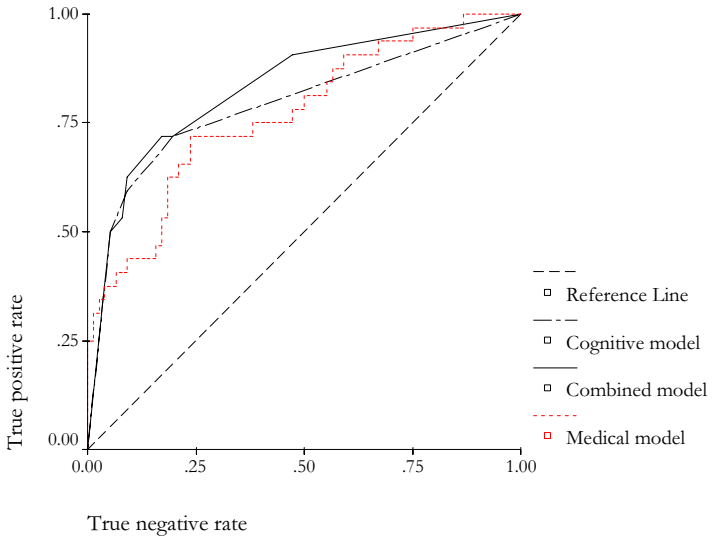


FIGURE 3. ROC curves of regression models predicting cognitive outcome.

TABLE 2. Univariate analyses.

| | Cognition | Basic ADL | Instrumental ADL |
|---|---|---|---|
| Demographic characteristics | | | |
| Age, years | **1.03 (1.00 to 1.06)** | **1.04 (1.0 to 1.08)** | 1.02 (.99 to 1.05) |
| High education | **.32 (.13 to.77)** | **.39 (.14 to 1.10)** | **.35 (.13 to .92)** |
| Sex, female | **3.66 (1.56 to 8.61)** | 1.35 (.52 to 3.52) | .48 (.19 to 1.18) |
| Vascular risk factors | | | |
| Hypertension | 1.52 (.67 to 3.47) | 1.53 (.59 to 4.01) | 1.23 (.51 to 2.95) |
| Diabetes mellitus | 2.5 (.74 to 8.41) | 1.63 (.39 to 6.74) | 1.14 (.28 to 4.65) |
| Hypercholesterolaemia | 1.04 (.36 to 3.01) | .19 (.02 to 1.50) | .55 (.15 to 2.07) |
| Transient ischaemic attack | 1.41 (.47 to 4.27) | .54 (.11 to 2.59) | 2.03 (.66 to 6.24) |
| Smoking in past five years | .95 (.41 to 2.18) | .80 (.29 to 2.20) | 1.29 (.53 to 3.12) |
| Regular alcohol consumption | **.34 (.09 to 1.24)** | .43 (.09 to 2.01) | .47 (.13 to 1.75) |
| Medical status at baseline | | | |
| MBI < 19 | **2.85 (1.15 to 7.09)** | **5.11 (1.40 to 18.61)** | **27.30 (3.54 to 210.73)** |
| NIHSS > 7 | 1.46 (.61 to 3.45) | **4.77 (1.75 to 13.01)** | **3.57 (1.43 to 8.90)** |
| Temperature > 38% C | **3.10 (1.13 to 8.55)** | **4.20 (1.42 to 12.41)** | **2.68 (.95 to 7.60)** |
| Glucose level (mmol/L) | **1.21 (.99 to 1.48)** | **1.19 (.99 to 1.45)** | 1.01 (.90 to 1.14) |
| Cholesterol level (mmol/L) | .86 (.62 to 1.20) | 1.22 (.83 to 1.81) | .99 (.70 to 1.40) |
| Systolic blood pressure (mmHg) | 1.0 (.99 to 1.01) | 1.00 (.99 to 1.02) | 1.00 (.99 to 1.02) |
| Diastolic blood pressure (mmHg) | .99 (.96 to 1.01) | 1.01 (.98 to 1.04) | 1.02 (.99 to 1.05) |
| Weakness of arm or leg | 1.41 (.61 to 3.25) | **2.66 (.89 to 7.90)** | **2.29 (.87 to 6.01)** |
| CT or MRI characteristics | | | |
| Stroke type | | | |
| PICH vs. infarct | .75 (.204 to 2.75) | .61 (.15 to 2.52) | .35 (.09 to 1.25) |
| Vascular territory | | | |
| Anterior vs. vertebrobasilar | 2.17 (.14 to 32.53) | 3.00 (.18 to 50.78) | 8.0 (.53 to 120.65) |
| Media vs. vertebrobasilar | 2.64 (.69 to 10.20) | 1.92 (.39 to 9.50) | 1.31 (.33 to 5.22) |
| Posterior vs. vertebrobasilar | 1.08 (.18 to 6.44) | 0.43 (.03 to 5.33) | 1.46 (.26 to 8.01) |
| Stroke location | | | |
| Left vs. brainstem/cerebellum | 2.79 (.70 to 11.16) | 1.08 (.20 to 5.89) | .34 (.08 to 1.46) |
| Right vs. brainstem/cerebellum | 1.88 (.46 to 7.72) | 2.06 (.40 to 10.69) | 1.69 (.46 to 6.23) |
| Right vs. left | .67 (.28 to 1.63) | 1.92 (.67 to 5.51) | **5.04 (1.65 to 15.43)** |
| Silent infarct(s) | 1.19 (.37 to 3.88) | .63 (.13 to 3.07) | .75 (.19 to 2.92) |
| Cerebral atrophy | .78 (.19 to 3.13) | **5.07 (1.30 to 19.69)** | 2.09 (.54 to 8.09) |
| White matter lesions | 2.33 (.81 to 6.67) | 1.34 (.39 to 4.62) | 1.33 (.42 to 4.18) |
| Lesion volume ($cm^3$) | **1.02 (1.01 to 1.04)** | **1.02 (1.00 to 1.04)** | **1.02 (1.01 to 1.04)** |
| Cognitive impairments at baseline | | | |
| Abstract reasoning | **15.39 (5.41 to 43.73)** | 1.80 (.63 to 5.13) | 1.47 (.55 to 3.92) |
| Language | **8.76 (3.13 to 24.51)** | **2.91 (1.03 to 8.26)** | **2.57 (.95 to 6.93)** |
| Executive functioning | **9.33 (3.65 to 23.89)** | **8.23 (2.78 to 24.32)** | **4.77 (1.87 to 12.19)** |
| Verbal memory | **7.19 (2.64 to 19.59)** | **3.2 (1.12 to 9.18)** | 1.52 (.55 to 4.23) |
| Visual memory | **5.09 (1.75 to 14.78)** | **15.32 (4.65 to 50.60)** | **11.39 (3.63 to 35.73)** |
| Visual perception/ construction | **6.22 (2.54 to 15.26)** | **11.91 (3.84 to 36.91)** | **18.04 (6.10 to 53.35)** |
| Unilateral neglect | **3.68 (1.08 to 12.60)** | **8.10 (2.25 to 29.14)** | **8.11 (2.21 to 29.77)** |

Values are Odds Ratios (95% CIs). Variables with $p \leq 0.1$ are printed in bold. PICH = primary intracerebral haemorrhage; NIHSS = National Institutes of Health Stroke Scale; MBI = modified Barthel Index.

TABLE 3. Multivariate odds ratios for all models (N=111).

| Cognition | Medical model | | Cognitive model | | Combined model | |
|---|---|---|---|---|---|---|
| | O.R. | 95%CI | O.R. | 95%CI | O.R. | 95%CI |
| Male sex | 0.16 | 0.06 -0.45 | | | 0.30 | 0.10-0.91 |
| Lesion volume | 1.04 | 1.02-1.06 | | | - | - |
| Age | 1.05 | 1.01-1.09 | | | - | - |
| Abstract reasoning | | | 6.64 | 1.48-22.73 | 4.49 | 1.19-16.96 |
| Executive functioning | | | 5.21 | 1.57-17.33 | 6.53 | 1.80-23.70 |
| AUC of ROC | 0.77 | 0.68-0.85 | 0.79 | 0.69-0.90 | 0.83 | 0.75-0.90 |
| GOF | p=0.20 | | | p=0.99 | p=0.88 | |

| Basic ADL | Medical model | | Cognitive model | | Combined model | |
|---|---|---|---|---|---|---|
| | O.R. | 95%CI | O.R. | 95%CI | O.R. | 95%CI |
| NIHSS > 7 | 11.44 | 2.69-48.63 | | | - | - |
| Age | 1.12 | 1.04-1.20 | | | - | - |
| Glucose level | 1.25 | .98-1.59 | | | 1.21 | 0.99-1.50 |
| Temperature > 38°C | 9.11 | 1.82-45.69 | | | - | - |
| Unilateral neglect | | | 17.26 | 3.10-96.07 | 17.75 | 2.77-113.71 |
| Visual memory | | | 16.12 | 3.99-65.11 | 22.09 | 5.01-97.48 |
| AUC of ROC | 0.79 | 0.70-0.87 | 0.84 | 0.73-0.96 | 0.85 | 0.77-0.91 |
| GOF | p=0.29 | | p=0.55 | | p=0.74 | |

| Instrumental ADL | Medical model | | Cognitive model | | Combined model | |
|---|---|---|---|---|---|---|
| | O.R. | 95%CI | O.R. | 95%CI | O.R. | 95%CI |
| Right vs. left hemisphere | 7.45 | 2.12-26.21 | | | 14.24 | 2.20-92.03 |
| MBI<19 | 35.50 | 4.27-294.59 | | | 26.17 | 2.26-303.16 |
| Perception/construction | | | 21.60 | 6.65-70.18 | 27.03 | 4.88-149.67 |
| AUC of ROC | 0.86 | 0.78-0.93 | 0.81 | 0.71-0.91 | 0.93 | 0.86-0.97 |
| GOF | p=0.99 | | - | | p=0.88 | |

Values are Odds Ratios and 95% CIs. Abbreviations: AUC=Area under the curve; ROC=Receiver Operating Characteristic; GOF=Hosmer and Lemeshow Goodness-of-Fit statistic; NIHSS=National Institutes of Health Stroke Scale; MBI = modified Barthel Index.

### DETERMINANTS OF FUNCTIONAL IMPAIRMENT ON THE LONG TERM

An MBI score <19 at follow-up was univariately associated with older age, lower education, a higher score on the baseline NIHSS, a lower score on the baseline MBI, body temperature > 38º C, admission glucose level, weakness in either arm or leg, large lesion volume, presence of cerebral atrophy, unilateral neglect, and impairments in language, verbal memory, executive functioning, visual memory, and visual perception and construction at baseline (all $p \leq 0.1$) (Table 2). In the medical model,

remaining basic ADL disturbances were independently associated with stroke severity at admission, older age, body temperature >38° C, and admission glucose level. The cognitive model retained two independent predictors, that is visual memory and unilateral neglect (Table 3). In the combined model, incomplete basic ADL recovery was associated with impairments in visual memory and unilateral neglect, and with admission glucose level. All other predictor variables dropped from this model because they failed to reach statistical significance. Patients with acute unilateral neglect had 18-fold greater odds and patients with acute visual memory impairments showed 22-fold greater odds for remaining basic ADL disturbances (Table 3). All models demonstrated an acceptable fit by the Hosmer-Lemeshow test. The combined and the cognitive model demonstrated the largest AUC (Figure 4). However, the difference between the three models did not reach significance.

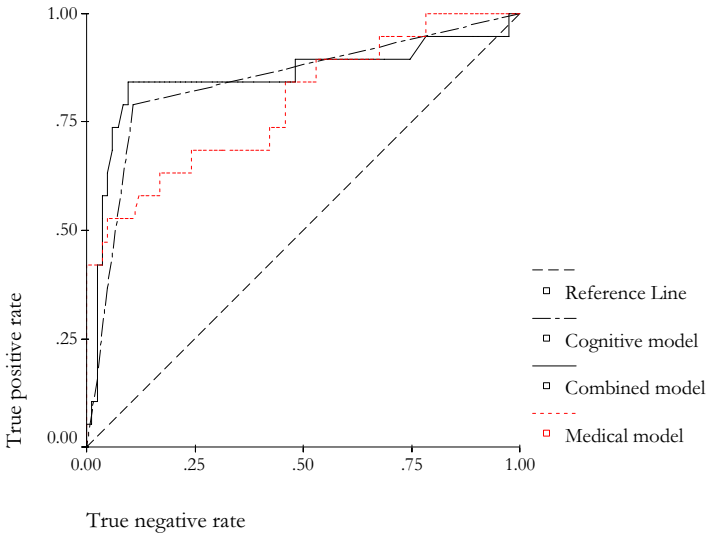


FIGURE 4. ROC curves of regression models predicting basic ADL dependence.

Instrumental ADL impairment on the long term was associated with a low level of education, poorer NIHSS and MBI at baseline, body temperature > 38° C, weakness in arm or leg, stroke location in the right hemisphere, lesion volume, unilateral neglect, and impairments in language, executive functioning, visual memory, and visual perception and construction at baseline (all $p \leq 0.1$) (Table 2). In the medical model, instrumental ADL impairment was independently associated with a poor MBI at

admission and a lesion location in the right hemisphere, whereas the cognitive model yielded only one predictor, i.e. visual perception and construction. In the combined model, instrumental ADL impairment was associated with impairments in visual perception and construction at baseline, poor MBI at baseline, and a lesion location in the right hemisphere. Patients with acute visual perceptual disorders demonstrated 27-fold greater odds of obtaining an adverse instrumental functional outcome (Table 3). The models demonstrated an acceptable fit by the Hosmer-Lemeshow test (no goodness-of-fit statistic could be calculated for the cognitive model as this model consisted of only one predictor). The combined model demonstrated a larger AUC than the medical model ($p<0.05$) and the cognitive model ($p<0.05$) (Figure 5).

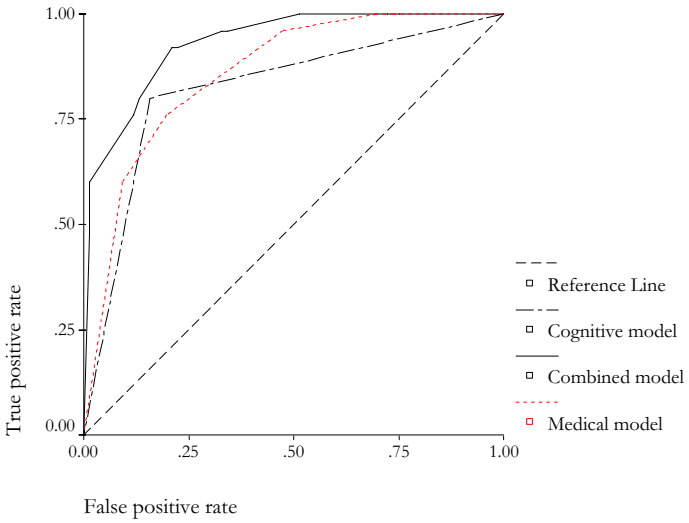


FIGURE 5. ROC curves of regression models predicting instrumental ADL dependence.

## DISCUSSION

In the present study, we examined the predictive value of a neuropsychological examination in the very early phase post-stroke with respect to long-term cognitive and functional impairment. Although it has been suggested that during the acute phase after stroke patients are often unstable and difficult to test (Laska et al., 2001; Lezak et al., 2004), our results show that an early neuropsychological examination is feasible in the majority of patients and has an important prognostic value regarding clinically relevant outcomes.

Of the included patients, 49% showed cognitive impairment in the first three weeks after stroke. Impairments in executive functioning and visual perception were the most frequent at this stage, whereas visual memory and neglect were present in less than 20% of patients. After the first six months post-stroke, 31% of patients still showed cognitive impairment, which is comparable to a previous hospital-based study that reported cognitive impairment in 35% of patients with first-ever stroke (Tatemichi et al., 1994). Nineteen percent of our patients demonstrated remaining disturbances in basic ADL on the long term, whereas twenty-four percent of patients were unable to keep up with more complex activities in daily life, such as grocery shopping, reading, and household management. The low prevalence of adverse functional outcome in our patient population together with the relatively low median NIHSS score at baseline indicates that our study population consisted of a rather mild stroke population. This was largely due to two factors: first, we only included patients with first-ever stroke because we wanted to rule out confounding factors related to outcome such as pre-existent cognitive impairment or ADL dependence. Second, patient attrition was inevitable given that we examined patients within the first three weeks post-stroke. Neuropsychological examination was not feasible in 12% of patients with acute first-ever stroke due to severe impairments in communication and consciousness. Moreover, the 57 patients who were not examined at follow-up had more severe impairments at baseline than patients who completed follow-up. This selection bias most probably resulted in an underestimation of the frequency of cognitive and functional impairment on the long term after stroke. Therefore, our findings cannot be directly generalised to the whole population of first-ever stroke patients. Still, our results may be useful in clinical practice because in the early stage of stroke prognosis and adequate allocation of rehabilitation resources are often very difficult. Our study shows that an early detailed neuropsychological examination can provide important prognostic information on both cognitive and functional outcome in this stroke population, and for instrumental ADL outcome even beyond that of demographic factors, lesion characteristics, vascular risk factors, and clinical status at baseline. In contrast to previous studies that have either used cognitive screening instruments such as the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) or the CAMCOG (De Koning et al., 1998), or focused on isolated cognitive deficits in acute stroke (Appelros et al., 2002; Hillis et al., 2003; Kalra et al., 1997; Laska et al., 2001; Pedersen et al., 2001), we submitted patients to a detailed neuropsychological examination covering the whole cognitive spectrum. Therefore, we were able to provide specific information regarding which acute cognitive disorders have the largest prognostic power. Different cognitive deficits were found to be important for cognitive and functional outcome. Impairments in more complex cognitive

functioning, i.e. reasoning and executive functioning, were independent predictors of cognitive impairment on the long term, while more perceptual and attentional dysfunctions were independent predictors of functional impairment at follow-up.

In our study, patients with executive impairments at baseline had nearly 7-fold greater odds of being cognitively impaired six months later than patients without executive disorders. The term executive function is used as an umbrella for various complex cognitive processes (such as task-switching, planning, fluency, inhibition) involved in achieving a particular goal (Elliott, 2003). Tasks tapping executive functions not only activate prefrontal regions in the brain, but also subcortical structures (e.g. striatal structures and thalamus) and cerebellar areas (Elliott, 2003; Vataja et al., 2003). Executive performance has also been reported to be an excellent predictor of vascular dementia in vascular compromised patients and stroke patients (Pohjasvaara, Mantyla, Ylikoski, Kaste, & Erkinjuntti, 2003; Roman & Royall, 1999). Interestingly, a recent study suggested that executive dysfunction might start insidiously before the first onset of symptomatic ischemic episodes in CADASIL (Amberla et al., 2004). It should be noted that global cognitive screening measures such as the MMSE often do not include items that assess executive functioning. Since executive dysfunction is one of the most frequent impairments in the early phase post-stroke and an excellent predictor of long-term outcome, we recommend the assessment of executive functioning in the early phase of stroke.

Other important independent predictors of long-term cognitive impairment in our study were lesion volume, age, and sex. The relation with female sex has been reported previously (Tatemichi et al., 1994). Lesion volume was an independent predictor of cognitive impairment, but no association with lesion location could be demonstrated. These findings are probably due to the fact that cognitive outcome was dichotomised as complete recovery vs. remaining cognitive impairment, independent of how many and which specific cognitive domain(s) were affected. It is likely that localised areas in the brain do play a role in disparate specific cognitive impairments on the long term after stroke (Ferro, 2001).

The predictive value of unilateral neglect and perceptual-related impairments with respect to functional impairment has been reported previously (Kalra et al., 1997). However, this is the first study to examine the predictive power of these impairments in a model covering all major cognitive domains in combination with other important factors such as lesion volume or demographic characteristics. Neglect and perceptual impairments proved to be the most important independent prognostic factors of functional outcome. Interestingly, the presence of acute neglect predicted long-term functional outcome in a very strong way, even though the majority of patients with acute neglect spontaneously recovered by the time of the follow-up examination.

These findings indicate that the long-term disability in the acute neglect group is not directly related to persistent neglect, in line with previous findings (Kinsella & Ford, 1985). Moreover, the prominent prognostic role of acute perceptual disorders cannot be explained indirectly by the fact that right hemispheric patients are at a greater risk of poor outcome, since both the location of the lesion and the presence of perceptual impairment were independent predictors of long-term functional impairment. Speculatively, the strong impact of perceptually related disorders on long-term functional outcome might have to do with the typical pattern of reduced awareness in these patients. Unfortunately, few studies have addressed the prognostic value of reduced awareness or 'anosognosia' after acute stroke (Appelros et al., 2002; Hartman-Maeir, Soroker, & Katz, 2001). This is mainly due to the lack of instruments for evaluating anosognosia and because of the heterogeneous nature of the disorder (Vuilleumier, 2004). Similarly, until this moment no scoring system for apraxia has been generally accepted. Diagnosis mainly relies on personal experience, clinical impression and intuition. Future studies are warranted to evaluate the relative contribution of these cognitive disorders in predicting long-term outcome after stroke.

Finally, our study confirms the prognostic importance of the patients' glucose level at admission. Increasing admission glucose level was an independent predictor of basic ADL functioning on the long term as has been reported previously (Baird et al., 2003; Bruno et al., 2002), and was also univariately associated with cognitive impairment on the long term. It is well established that acute stress situations such as stroke can cause hyperglycaemia, which in turn may lead to infarct expansion in the case of ischaemic stroke (Baird et al., 2003; Bruno et al., 2002), or more profound brain oedema and perihaematomal cell death in the case of intracerebral haemorrhage (Song et al., 2003). Hyperglycaemia in acute stroke often occurs without pre-existing diagnosis of diabetes mellitus (Bruno et al., 2002). Indeed, history of diabetes mellitus was not associated with functional or cognitive outcome in our study.

Some limitations of this study should be addressed. In order to maximise comparability between CT and MRI, a rather basic method was used for rating cerebral atrophy. This method is less detailed than volumetric methods, and therefore the predictive value of cerebral atrophy regarding long-term cognitive or functional outcome might have been underestimated. Moreover, the results of this study must be considered to be preliminary given that the number of patients and more specifically the outcomes of interest on which our models were generated were relatively small. This may have resulted in false-positive predictor variables, or alternatively in important variables being missed because of multicollinearity or lack of power. Furthermore, these models have only been tested in the data set from which they have

been derived. They have not been validated in an independent cohort of acute first-ever stroke patients. Validation of these models in similar patient populations is needed in future research.

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# Chapter 5

## Domain-specific Cognitive Recovery after First-ever Stroke

### A follow-up study of 111 cases

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## ABSTRACT

*Objective* Cognitive disorders in the early phase after stroke are common and have been associated with long-term disability and post-stroke dementia. No data exist on the prognosis of specific acute cognitive disorders because of uncertainty about the predictive value of early cognitive testing. Moreover, it is unclear which factors influence cognitive recovery after stroke.

*Methods* We followed the course of cognitive functioning in 111 patients with a first-ever stroke and 77 healthy controls by administering two subsequent neuropsychological examinations with a 6 to 10 months interval (mean interval, 7.5 ± 1.3 months). The patients underwent the baseline neuropsychological examination within the first three weeks post-stroke (mean interval, 7.9 ± 4.2 days). In order to examine potential predictors of domain-specific cognitive recovery, we also recorded vascular risk factors, clinical variables, and lesion characteristics.

*Results* Overall, 49% of patients were cognitively impaired in the early phase of stroke, with disorders in visual perception/construction and executive functioning being the most prevalent (32%). On the whole, cognitively impaired patients showed an improvement in all cognitive domains at follow-up. Recovery in visual perception/ construction and visual memory was the most common (83% and 78%, respectively), whereas recovery in abstract reasoning and language was the least frequent (41% and 54%, respectively). Patients who were cognitively intact in the early phase of stroke still showed about the same long-term cognitive performance as healthy controls. Domain-specific cognitive functioning in the early phase of stroke significantly predicted cognitive functioning in the same domain at follow-up, except for visual perception and construction. Instead, an executive disorder was a better predictor of long-term perceptual/ constructional disability (O.R.=5.3; 95%CI = 1.9-24.0). Although language performance significantly predicted a long-term deficit in the same domain (O.R.=6.5; 95%CI=1.6-27.4), abstract reasoning appeared to be a better predictor of long-term language performance (O.R.=39.9; 95%CI = 3.7-426.9). Factors associated with poor cognitive recovery in multiple domains were age (all $p \leq 0.006$), pre-existent verbal ability (all $p \leq 0.004$), and lesion locations involving the temporal (all $p \leq 0.016$) and occipital lobe (all $p \leq 0.05$). Lesion volume ($p < 0.001$), diabetes mellitus ($p = 0.02$) and a lesion location involving the frontal lobe ($p = 0.02$) compromised recovery in a single cognitive domain.

*Conclusion* An early neuropsychological examination provides valuable information on long-term cognitive performance. The prognosis of acute higher-level visual disorders is the most favourable, while recovery with respect to abstract reasoning and language is less common. Cognitive recovery is associated with age, pre-existent ability, lesion volume, lesion location, and diabetes mellitus.

## INTRODUCTION

Cognitive dysfunction is a common sequel of stroke and affects up to two thirds of patients (Ballard et al., 2003). In the acute phase of stroke cognitive impairment is related to direct local effects of the stroke, but also to hypoperfusion (Hillis et al., 2004; Hillis, Wityk, Barker, Ulatowski, & Jacobs, 2003) and functional deactivation (diaschisis) in nearby or remote areas of the brain (Ferro, 2001). Large variability in cognitive function exists among acute stroke patients, depending in part on the location and size of the lesion. Moreover, the degree of cognitive recovery within the first months after stroke varies considerably across patients (Ballard, Rowan, Stephens, Kalaria, & Kenny, 2003; Rasquin et al., 2004). Early diagnosis and prediction of the potential for recovery from cognitive deficits such as amnesia or executive dysfunction could be of great importance for determining an appropriate discharge destination and for guiding rehabilitation therapy.

While previous studies have demonstrated that a global cognitive deterioration within the first three months post-stroke is a good predictor of an adverse functional outcome (Galski, Bruno, Zorowitz, & Walker, 1993; Mok et al., 2004; Tatemichi et al., 1994) and post-stroke dementia (Lin et al., 2003), it is not known whether a detailed evaluation of specific cognitive functions in the early phase of stroke can give valid and specific information about domain-specific cognitive functioning in the long term. Moreover, the prevalence of cognitive recovery and the cognitive abilities most likely to recover have not been adequately investigated, and it is unclear which clinical factors influence cognitive recovery after stroke. To our knowledge, only three studies (Desmond, Moroney, Sano, & Stern, 1996; Hochstenbach, Den Otter, & Mulder, 2003; Patel, Coshall, Rudd, & Wolfe, 2003) examined potential predictors of cognitive recovery. In these studies an association was demonstrated with smoking (Patel et al., 2003), unilateral neglect (Patel et al., 2003), diabetes mellitus (Desmond et al., 1996), lowered consciousness at hospital admission (Hochstenbach et al., 2003), and lesion side (with evidence of either a left hemisphere (Desmond et al., 1996) or a right hemisphere advantage (Hochstenbach et al., 2003; Patel et al., 2003). However, these studies suffered from a number of methodological shortcomings. *First*, baseline examination was typically performed at three months post-stroke or even at a later stage. Given that the largest improvement in cognitive functioning occurs within the first three months after stroke (Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001; Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1995), the prevalence and degree of cognitive recovery may have been underestimated and several factors possibly associated with recovery may have been disregarded. *Second*, most longitudinal stroke studies (Hochstenbach et al., 2003; Patel et al., 2003) did not include a re-examination

of the control group although this is crucial to control for potential practice effects and statistical artefacts. *Third,* none of the aforementioned studies have examined pre-existent cognitive functioning of stroke patients. Therefore, these studies may have included patients with pre-existent dementia or cognitive decline not related to the stroke, which has been shown to be present in about one sixth of stroke patients (Henon et al., 1997). *Finally*, these studies typically evaluated the prevalence of cognitive recovery in a cohort of stroke patients that included patients without cognitive disturbances (Desmond et al., 1996; Hochstenbach et al., 2003; Patel et al., 2003). Yet, such patients already perform very well at the baseline assessment and are therefore not likely to show improvement at the follow-up examination. Alternatively however, initially intact patients might show a subtle insidious decline in cognitive performance as compared to healthy controls. Therefore, it might be important to follow the cognitive recovery course separately in patients with cognitive impairment at baseline and those without impairment.

The aim of the present study was threefold: (i) to evaluate the prevalence and nature of cognitive recovery during the first months after stroke, (ii) to examine the predictive value of a neuropsychological examination in the early phase of stroke with respect to domain-specific cognitive functioning after six months, and (iii) to find factors associated with domain-specific cognitive recovery.

In the present study, the baseline neuropsychological assessment was performed within the first three weeks post-stroke. We followed the course of six distinct cognitive domains in three subject groups, i.e. healthy controls, patients who were cognitively intact at baseline, and patients who were cognitively impaired at baseline. To increase the probability that cognitive change would be related exclusively to stroke, our study population consisted of patients with first-ever stroke who had no pre-existent neurological, psychiatric, or cognitive abnormalities.

## Methods

### Subjects

The study population consisted of consecutive first-ever stroke patients admitted to stroke units of three hospitals in the Netherlands (St.-Elisabeth Hospital Tilburg, University Medical Centre Utrecht, and Tweesteden Hospital Tilburg) between December 2001 and October 2003. The diagnosis of stroke was based on the presence of both an acute focal deficit and an associated lesion on CT or MRI. Patients with a normal scan at admission underwent a second scan within the first week post-stroke.

Exclusion criteria were pre-existent dementia (as defined by a score of 3.6 or higher on the short Informant Questionnaire on Cognitive Decline in the Elderly – IQCODE Dutch Version) (De Jonghe, Schmand, Ooms, & Ribbe, 1997) and pre-existent neurological or psychiatric illnesses. Only native Dutch speakers were included, and all included subjects were younger than 85 years to avoid disproportional aging effects on cognitive performance. This procedure resulted in a population of 190 patients with acute first-ever stroke. In addition, we excluded patients who could not be neuropsychologically assessed within the first 21 days post-stroke on the majority of neuropsychological tasks to allow evaluation on at least 4 of 6 cognitive domains (N=22). Further exclusions between baseline and follow-up examination because of events that could potentially affect cognitive recovery (recurrent stroke, psychosis, or interventions for severe comorbidity such as chemotherapy or CABG) (N=26) and other dropout reasons (death, refusal, detention in prison, or moving abroad) (N=31) resulted in a study population of 111 patients. This population has been reported previously (Nys et al., 2005).

The control group consisted of subjects living in the community. The controls were either spouses or family of patients, or volunteers who came to our attention through advertising in newspapers or by word of mouth. We adopted the same exclusion procedure as for the patients, which resulted in a study population of 77 healthy controls. Control subjects were carefully matched to the stroke patients with respect to age and education.

The ethics committees of the three participating hospitals approved the study protocol. Informed consent was obtained from all participating subjects before inclusion in the study.

### LONGITUDINAL NEUROPSYCHOLOGICAL EXAMINATION

All subjects underwent two subsequent neuropsychological examinations. The baseline neuropsychological examination of the stroke patients was carried out within the first three weeks after the stroke (7.9 $\pm$ 4.2 days since stroke onset). All subjects, including controls, were re-examined with an extended neuropsychological examination after a minimum of 6 and a maximum of 10 months, dated from their original assessment (mean interval, 7.5 $\pm$ 1.3 months). The first assessment took about 1.5 hour, whereas the second extended examination lasted approximately 2.5 hours. Trained neuropsychologists performed the assessments. Subjects were given breaks where appropriate to minimise the effects of fatigue or motivation on performance.

Six major cognitive domains were assessed using both verbal and nonverbal neuropsychological tasks. The test battery was extended at the second examination in

order to have a more detailed representation of each domain. This resulted in the following test battery (tasks added to the second examination are presented in italics) (Lezak, Howieson, & Loring, 2004): (1) abstract reasoning: Raven Advanced Progressive Matrices (short form), Similarities (WAIS-III); (2) verbal memory: Rey Auditory Verbal Learning Test, Digit Span (WAIS-III), *Wechsler Memory Scale – Story Recall A;* (3) attention and executive functioning: Brixton Spatial Anticipation Test, Visual Elevator (Test of Everyday Attention) (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994), letter fluency, *Stroop Colour Word test, Semantic Fluency, Zoo test (BADS)*; (4) visual perception and construction: Judgement of Line Orientation (short form), Test of Facial Recognition (short form), Rey-Osterrieth Complex Figure–copy, *WAIS-III block* patterns; (5) visual memory: Corsi Block Span, Rey-Osterrieth Complex Figure-delay, *Wechsler Memory Scale-Visual Reproduction, Location Learning Task* (Kessels, Nys, Brands, & van Zandvoort, 2004); (6) language: Token Test (short form), Boston Naming Test (short form), *Chapman Reading Task*.

### Transformation of neuropsychological test results

Two types of variables were calculated from these test results: (i) Summary scores for the six cognitive domains were constructed for use in analyses to enhance reliability and to reduce the number of variables (Lezak et al., 2004). Each domain score was created by converting the raw scores from the individual tests to standardised scores (z-scores) based on the means and standard deviations of the control group on the first and second examination. Subsequently, we averaged z-scores of tasks belonging to the same cognitive domain, in which a lower domain score indicates worse performance. (ii) The prevalence of domain-specific disorders at baseline and at follow-up was calculated. A disorder was considered to be present whenever a patients' domain score was lower than -1.65, which is associated with the 0.05 level of statistical significance (Clark-Carter, 1997).

### Potential correlates of domain-specific cognitive recovery

*Demographic characteristics and pre-existent ability*

We recorded the age and sex of all subjects. Level of education was scored using a Dutch classification system according to Verhage, ranging in ascending order from 1 (less than primary school) to 7 (university degree). Pre-existent verbal ability was estimated by means of the National Adult Reading Test (NART-Dutch Version) (Schmand, Bakker, Saan, & Louman, 1991) at the follow-up examination. This measure is known to be relatively unaffected by neurological disorder (Crawford, Parker, & Besson, 1988; Watt & O'Carroll, 1999), also when verbal skills are affected

by brain damage (Crawford et al., 1988; Schmand et al., 1991). Particularly in older subject samples, this is a better measure of pre-existent ability than the level of education.

*Stroke lesion characteristics*

Lesion characteristics were determined from CT or MRI by an experienced stroke neurologist (HBvdW) who was blind for the clinical data. Stroke type (infarct, haemorrhage), lesion location (supratentorial, infratentorial), lesion side of supratentorial lesions (left, right), cortical or subcortical lobe involvement (frontal, parietal, temporal, occipital), subcortical grey matter involvement (caudate nucleus, striatum, thalamus) and infratentorial involvement (brain stem, cerebellum) were recorded. In addition, lesion volume was calculated with Leica Q500 MCP image analysis software by manual tracing of the lesion on each slice on which the infarct or intracerebral haemorrhage was present. This method is described in detail elsewhere and has been shown to have a high inter-rater reliability (Van der Worp et al., 2001). Finally, the presence of pre-existent brain pathology was recorded by using straightforward dichotomous ratings suitable for use with both CT and MRI. We rated (i) pre-existent silent infarcts (classified as present when an infarct was found in the brain that could not have caused the actual neurological deficits and if the patient, family, or medical record did not describe a prior corresponding stroke episode) (Nys et al., 2005), (ii) white matter lesions (scored as present if patients obtained a score > 0 on the Van Swieten scale) (Van Swieten, Koudstaal, Visser, Schouten, & Van Gijn, 1988), and (iii) cortical atrophy (classified as present when a generalised dilatation of cortical sulci was found) (Nys et al., 2005).

*Vascular risk factors*

We recorded the presence of vascular risk factors on the basis of the medical history and medication use (history of diabetes mellitus, hypertension, hypercholesterolaemia, transient ischaemic attack), and recorded whether patients had a history of smoking during the last five years and if they had an alcohol consumption of more than two units per day.

*Clinical status at baseline*

Stroke severity at baseline was assessed by means of the National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989). The presence and severity of depressive symptoms at baseline was measured with the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979). The MADRS is an observer-rated scale ranging from 0 (no depressive symptoms) to 60 (severe depressive symptoms),

which is not heavily relying on somatic symptoms. The degree of unilateral inattention in the early phase of stroke was assessed by means of the Star Cancellation (Wilson, Cockburn, & Halligan, 1987), which is a cancellation task ranging from 0 (patient neglected all items) to 54 (patient cancelled out all items).

### Statistical analyses

We evaluated differences among patients who were cognitively intact at baseline and those who were not by comparing clinical and demographic characteristics in both groups using $\chi^2$ tests for categorical data, Mann-Whitney U Tests for ordinal data, and student t-tests for continuous data.

The longitudinal change in cognitive performance was calculated by comparing the difference in domain scores between the baseline and follow-up examination. Positive difference scores indicate improvement, whereas negative difference scores indicate decline from baseline. Scores near zero indicate a change that equals the mean control group change (which is zero as a result of our standardisation method). A univariate analysis of variance (ANOVA) was performed to compare the extent of cognitive change in the six cognitive domains between controls, patients who were cognitively intact at baseline and patients who were cognitively impaired at baseline. Next, logistic regression analyses were performed to evaluate the predictive value of early cognitive testing with respect to cognitive functioning in the long term. Therefore, a series of hierarchical logistic regression analyses were performed with age, sex, and estimated pre-existent verbal ability (NART) entered in the first step and each acute cognitive deficit entered *separately* in the next step. A second series of hierarchical multiple logistic regression analyses were then performed to evaluate the relative contribution of the different cognitive disorders at baseline in the prediction of chronic cognitive deficits. Again, age, sex and NART were forced in the first step and all acute cognitive deficits were entered *simultaneously* in the next step in a forward stepwise fashion.

To identify independent predictors of domain-specific cognitive change, we used hierarchical multiple linear regression analyses with cognitive change scores as the dependent variables. Baseline cognitive performance and demographic variables were entered in the first step; candidate predictor variables were then entered separately in the next step. Finally, to identify the most important independent predictors of domain-specific recovery, all variables with significant univariate associations ($p<0.05$) were entered together in a multivariate stepwise regression analysis for each cognitive domain.

## RESULTS

### COGNITIVE DISORDERS IN THE EARLY PHASE OF STROKE

The clinical and demographic characteristics of the patient population are shown in Table 1, classified according to intact or impaired cognitive functioning at baseline. Fifty-four of 111 patients (49%) were cognitively impaired in one or more domains in the first weeks after stroke, with a mean of 3 impaired domains per patient [range: 1-6]. More specifically, 36 of 111 patients (32.4%) demonstrated a disorder in visual perception and construction, 35 patients (31.5%) in executive functioning, 27 patients (24.3%) in abstract reasoning, 24 patients (21.6%) in language, 24 patients (21.6%) in verbal memory, and 18 patients (16.2%) in visual memory (Figure 1). Patients with an intact cognition at baseline demonstrated a higher level of education and a smaller lesion volume than patients who were cognitively impaired in the early phase of stroke (Table 1).

TABLE 1. Patient characteristics at baseline.

| Characteristics | Entire population (N=111) | Intact cognition (N=57) | Impaired cognition (N=54) | p |
|---|---|---|---|---|
| Demographics | | | | |
| Age (years), mean ± SD | 60.1 ± 14.2 | 59.5 ± 14.2 | 60.8 ± 14.2 | 0.63 |
| Education, median [range] | 4 [0-7] | 5 [2-7] | 4 [1-7] | 0.001* |
| Sex, male | 54.1 | 40.4 | 51.9 | 0.22 |
| Stroke lesion characteristics | | | | |
| % infarct / all strokes | 90.1 | 94.7 | 85.2 | 0.09 |
| Lesion volume (ml), mean ± SD | 17.8 ± 29.2 | 8.8 ± 16.2 | 27.4 ± 36.3 | 0.001* |
| % supratentorial /all strokes | 84.8 | 80.4 | 89.6 | 0.20 |
| % left / left and right strokes | 51.7 | 53.3 | 50.0 | 0.74 |
| Pre-existent pathology | | | | |
| White matter lesions | 15.3 | 15.8 | 14.8 | 0.89 |
| Silent infarct(s) | 13.7 | 17.0 | 10.2 | 0.32 |
| Cerebral atrophy | 10.7 | 11.3 | 10.0 | 0.83 |

Values are within-group percentages unless indicated otherwise. Some percentages are based on incomplete samples due to small amounts of missing data. Analyses are chi square analyses for categorical data, Mann-Whitney U Tests for ordinal data, and Student t-tests for continuous data between patients with intact and impaired cognition. * $p<0.05$.

## Prevalence of cognitive change between baseline and follow-up

*Initially impaired patients*

Patients with a small number of cognitive impairments at baseline demonstrated more often a complete cognitive recovery in the long term than patients with a more widespread cognitive impairment (Mann-Whitney U=172.5; p<0.001). The mean number of cognitive disorders per patient decreased from 3.0 [1-6] at baseline to 1.3 [0-5] at follow-up (p<0.001). Domain-specific recovery in visual perception/construction and visual memory was the most frequent (83% and 78%, respectively), whereas recovery in abstract reasoning and language was the least common (41% and 54.2%, respectively) (Figure 1). At follow-up, 1 patient (3.7%) had gained a disorder in abstract reasoning, 5 patients (16.7%) in language, 1 patient (3.3%) in verbal memory, 4 patients (11.1%) in visual memory, and 1 patient (5.6%) in visual perception and construction. There were no patients who gained a deficit in executive functioning. Altogether, this dissimilar pattern of recovery resulted in a neuropsychological profile at follow-up that was different from the early phase of stroke, with disorders in abstract reasoning being the most common and disorders in visual memory being the least common (9%) (Figure 1).

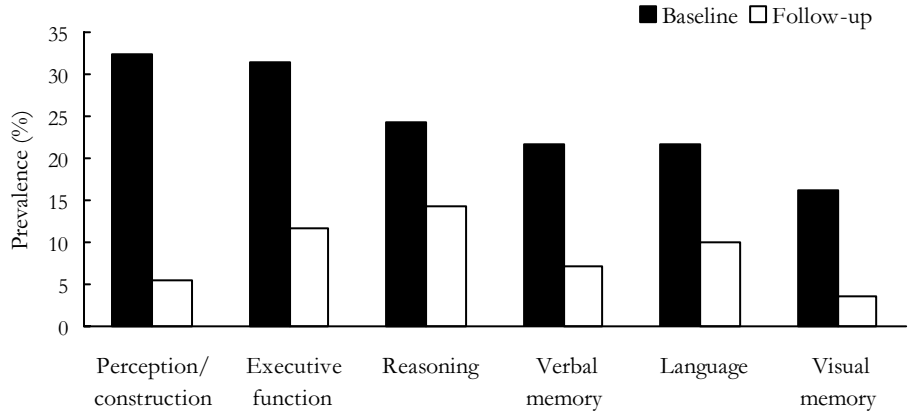


Figure 1. Prevalence of domain-specific cognitive impairment at baseline and follow-up

*Initially intact patients*

The majority of these patients (51/57 or 90%) remained cognitively intact in the long term. At follow-up, 3 patients (5.3%) had developed a deficit in abstract reasoning, 2 patients (3.5%) in executive functioning, 1 patient (1.8%) in visual memory, and 3

patients (5.3%) in visual perception/ construction. There were no initially intact patients who gained a deficit in verbal memory or language.

When comparing the degree of cognitive change between controls, initially intact and initially impaired patients by means of an ANOVA, a main effect of group was found with respect to all cognitive domains (all $p<0.01$). Post-hoc Dunnett tests revealed that the initially impaired group demonstrated a significant improvement in all cognitive domains as compared to healthy controls (all $p<0.05$). In contrast, the initially intact group showed the same longitudinal course as controls in all domains (Figure 2).

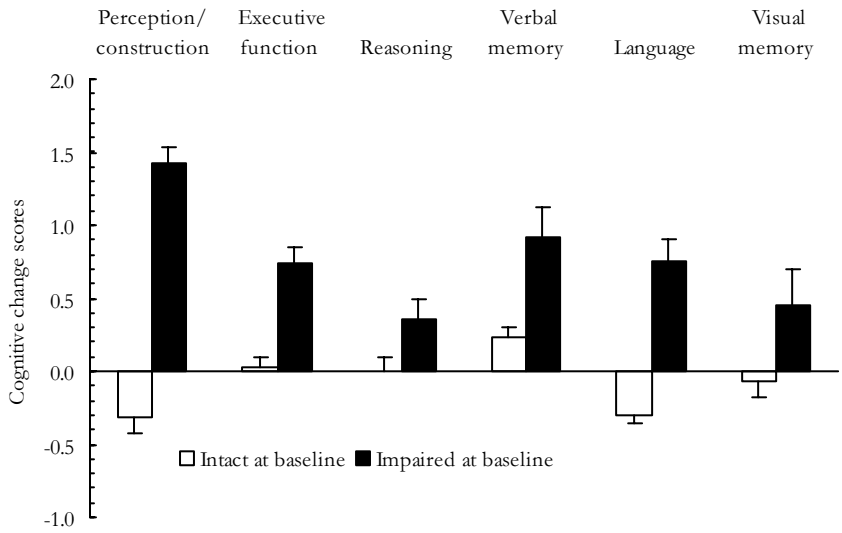


FIGURE 2. Level of cognitive change between baseline and follow-up. The X-axis represents the mean change in controls (zero).

### PREDICTIVE VALUE OF THE EARLY NEUROPSYCHOLOGICAL EXAMINATION

Logistic regression analyses adjusted for age, sex, and pre-existent verbal ability showed that patients with acute cognitive disorders were at risk for remaining impaired on the same cognitive domain at follow-up, except for visual perception and construction (Table 2). In addition, other cognitive domains at baseline significantly predicted performance in these domains, e.g. abstract reasoning was significantly predicted by abstract reasoning at baseline but also by language performance at baseline. Multivariate stepwise analyses demonstrated that cognitive functioning at

follow-up was best predicted by the same cognitive domain at baseline, except for two domains. Language was better predicted by abstract reasoning at baseline, and visual perception/ construction was better predicted by executive functioning at baseline (Table 2). Each model demonstrated a sufficient goodness-of-fit as measured with the Hosmer and Lemeshow goodness-of-fit test (all $p>0.05$) (Hosmer & Lemeshow, 1989).

### Clinical correlates of domain-specific cognitive recovery

All demographic variables, lesion characteristics, and vascular risk factors that are related to recovery in one or more cognitive domains are shown in Table 3. Important demographic characteristics associated with poor cognitive recovery were pre-existent verbal ability and age. Lesion characteristics associated with poor recovery were a larger lesion volume and lesion locations involving the frontal, temporal, or occipital lobe. Diabetes mellitus was the only vascular risk factor associated with a poor recovery in a single cognitive domain, i.e. abstract reasoning. Finally, the severity of unilateral neglect was related to a poor recovery in visual memory.

TABLE 2. Predictive value of domain-specific cognitive functioning in the early phase of stroke.

Univariate analyses

| | After six months | | | | | |
|---|---|---|---|---|---|---|
| < 3 weeks post-stroke | Reasoning | Language | Executive function | Verbal memory | Visual memory | Perception/ construction |
| Reasoning | 17.8 (2.8-111.9) | 20.4 (3.4-120.5) | - | - | - | - |
| Language | 8.2 (1.4-48.7) | 6.5 (1.6-27.4) | 4.2 (1.1-16.3) | - | - | - |
| Executive function | - | 5.2 (1.3-21.4) | 17.7 (3.3-95.2) | - | 5.3 (1.1-24.8) | 5.3 (1.2-24.0) |
| Verbal memory | - | - | 13.3 (2.9-60.2) | 21.9 (1.7-287.3) | 5.9 (1.2-28.4) | - |
| Visual memory | - | 9.6 (1.7-52.9) | 7.4 (1.6-33.4) | - | 5.9 (1.3-27.6) | - |
| Perception/construction | - | - | 8.2 (1.9-35.1) | - | 5.4 (1.2-25.2) | - |

Multivariate stepwise analyses

| | After six months | | | | | |
|---|---|---|---|---|---|---|
| < 3 weeks post-stroke | Reasoning | Language | Executive function | Verbal memory | Visual memory | Perception/ construction |
| Reasoning | 17.8 (2.8-111.9) | 39.9 (3.7-126.9) | - | - | - | - |
| Language | - | - | - | - | - | - |
| Executive function | - | - | 17.7 (3.3-95.2) | - | - | 5.3 (1.9-2.4) |
| Verbal memory | - | - | - | 21.9 (1.7-287.3) | - | - |
| Visual memory | - | 20.8 (1.9-230.4) | - | - | 5.9 (1.3-27.6) | - |
| Perception/construction | - | - | - | - | - | - |
| Nagelkerke $R^2$ entire model | 0.69 | 0.59 | 0.41 | 0.46 | 0.24 | 0.19 |

Values are Odds Ratios (95% CIs) adjusted for age, sex, and NART (National Adult Reading Test) score. Only significant values are reported ($p<0.05$).

TABLE 3. Predictors of domain-specific cognitive change – univariate analyses.

† Adjustment for baseline domain-specific cognitive functioning. ‡ Adjustment for baseline domain-specific cognitive functioning, age, and NART (National Adult Reading Test) score. Values are standardised beta's (p-values), and only values with $p<0.05$ are reported.

| | Reasoning | Executive function | Visual perception/ construction | Verbal memory | Visual memory | Language |
|---|---|---|---|---|---|---|
| Demographics† | | | | | | |
| Age, y | - | -.25 (.001) | - | -.14(.039) | -.23 (.004) | -.16 (.02) |
| Sex | - | - | - | - | - | - |
| NART | .46 (.001) | .26 (.001) | - | .29 (.000) | .24 (.004) | .38 (.001) |
| Vascular risk factors‡ | | | | | | |
| Hypertension | - | - | - | - | - | - |
| Diabetes | -.16 (.04) | - | - | - | - | - |
| Hypercholesterolaemia | - | - | - | - | - | - |
| TIA(s) | - | - | - | - | - | - |
| Smoking | - | - | - | - | - | - |
| Regular alcohol consumption | - | - | - | - | - | - |
| Lesion characteristics‡ | | | | | | |
| Volume | - | -.18(.02) | -.19 (.004) | - | -.34(.001) | - |
| Side | - | - | - | - | - | - |
| Lesion type | - | - | - | - | - | - |
| Supra-/Infratentorial | - | - | - | - | - | - |
| Involvement of | | | | | | |
| frontal lobe | -.16(.04) | - | -.20 (.003) | - | - | - |
| parietal lobe | - | - | - | - | - | - |
| temporal lobe | - | -.18 (.02) | -.13 (.05) | -.12 (.014) | -.19 (.02) | - |
| occipital lobe | - | - | -.16 (.01) | - | -.24 (.002) | - |
| Involvement of | | | | | | |
| thalamus | - | - | - | - | - | - |
| caudate | - | - | - | - | - | - |
| striatum | - | - | - | - | - | - |
| Involvement of | | | | | | |
| brain stem | - | - | - | - | - | - |
| cerebellum | - | - | - | - | - | - |
| Silent infarct(s) | - | - | - | - | - | - |
| White matter lesions | - | - | - | - | - | - |
| Cerebral atrophy | - | - | - | - | - | - |
| Mood at baseline‡ | - | - | - | - | - | - |
| Unilateral attention‡ | - | - | - | - | .24(.005) | - |
| Stroke severity‡ | - | - | - | - | - | - |

In the multivariate regression models (Table 4), pre-existent verbal ability was associated with recovery in 5 of the 6 cognitive domains. A younger age was associated with a good recovery in the two memory domains, language and executive functioning. Lesion location was more important than lesion volume in predicting the degree of domain-specific recovery, i.e. a lesion in the frontal lobe was independently associated with a poor recovery in visual perception and construction, a lesion in the temporal lobe with a poor recovery in executive function and verbal memory, and a lesion in the occipital lobe with a poor recovery in visual memory and visual perception/ construction. Lesion volume independently predicted the degree of recovery in visual memory. Finally, diabetes mellitus was independently related to a poor recovery in abstract reasoning.

TABLE 4. Predictors of domain-specific cognitive change – multivariate analyses.

| | Reasoning | Executive function | Perception/ construction | Verbal memory | Visual memory | Language |
|---|---|---|---|---|---|---|
| Demographics | | | | | | |
| Age, y | | -.25(.001) | | -.17(.001) | -.21 (.01) | -.18(.001) |
| NART | .44(.001) | .22 (.004) | | .26 (.001) | .21 (.004) | .35(.001) |
| Vascular risk factors | | | | | | |
| Diabetes | -.19 (.01) | | | | | |
| Lesion variables | | | | | | |
| Volume | | X | X | X | -.32(.001) | |
| Involvement | | | | | | |
| frontal lobe | X | | -.14(.02) | | | |
| parietal lobe | | | | | | |
| temporal lobe | | -.18 (.02) | | -.12 (.01) | | |
| occipital lobe | | | -.16 (.01) | | -.15 (.05) | |
| Neglect | | | | | X | |
| Adjusted $R^2$ | .38 | .48 | .64 | .76 | .52 | .81 |

Forward stepwise linear regression analyses with adjustment for baseline domain-specific cognitive functioning. Values are standardised beta's (p-values). X indicates predictors that do not reach significance in the multivariate model. NART denotes National Adult Reading Test.

## DISCUSSION

The main reason why previous studies have paid little attention to cognition in the early phase of stroke has been uncertainty about the reliability and predictive value of such an early examination. It has been argued that a number of stroke-related problems such as fatigue, fluctuating level of arousal, or emotional distress may exacerbate or obscure cognitive performance in this stage (Lezak et al., 2004). Nevertheless, the present study demonstrates that an early comprehensive neuropsychological examination can predict long-term cognitive performance in patients with a first-ever stroke. Therefore, such an examination could assist in a more appropriate allocation of rehabilitation resources. Moreover, interventions aimed at restoration and/ or compensation of impaired cognitive functions could start off in an earlier stage, which might be important for the effectiveness of the treatment (Biernaskie, Chernenko, & Corbett, 2004; Paolucci et al., 2000). There were two exceptions with respect to the specificity of the predictions, however. *First*, an executive disorder rather than perceptual performance in the early phase of stroke predicted the presence of a long-term perceptual/constructional deficit. While there is some evidence that executive dysfunction is related to the severity of unilateral neglect after stroke (Manly, Woldt, Watson, & Warburton, 2002; Rusconi, Maravita, Bottini, & Vallar, 2002), the present study shows that this also applies to visual perception and construction in general. Particularly the constructional component in this domain may benefit from an intact planning capacity and the ability to use structure (Elderkin-Thompson et al., 2004). *Second*, although a language disorder in the early phase of stroke significantly predicted the presence of a language deficit in the long term, abstract reasoning was a better predictor of long-term language performance. In a similar vein, previous studies have shown a close association between abstract reasoning impairment and aphasia (Baldo et al., 2005; De Renzi, Faglioni, Savoiardo, & Vignolo, 1966; Gainotti, D'Erme, Villa, & Caltagirone, 1986).

The majority of patients who were cognitively intact immediately after the stroke retained the same level of cognitive performance at follow-up as healthy controls, suggesting that there is no evidence of a generalised insidious cognitive deterioration in this stroke population, at least not in the first six months after the stroke. Nevertheless, it should be noted that a few of these patients developed new cognitive disorders as compared to baseline, which could be the consequence of increasing brain damage due to a growing amount of white matter lesions, cerebral atrophy, or silent infarcts (Vermeer et al., 2003). In addition, some of these patients might have been performing almost within the abnormal range but still above the cut-off point at baseline but below the cut-off point at follow-up.

Patients who were cognitively impaired in the early phase of stroke still performed worse than healthy controls at follow-up, especially if multiple cognitive disorders were present at baseline. Nevertheless, improvement as compared to baseline seemed to be the rule rather than the exception in all cognitive domains. Previous studies have reported global cognitive improvement rates ranging from 10% to 50% (Ballard et al., 2003; Desmond et al., 1996; Rasquin et al., 2004; Tham et al., 2002), depending primarily on the time interval between the stroke event and the neuropsychological assessments, and on the criteria used to define recovery. In the present study, domain-specific recovery occurred in 41% to 83% of cases, depending on the nature of the cognitive deficit. Recovery in the visual domains, i.e. in visual perception/construction and visual memory was the most prevalent, whereas recovery in abstract reasoning and language was the least common. The prevalence of recovery in our study was much higher than in the aforementioned studies, and this is probably related to the fact that our baseline assessment occurred at a much earlier stage, leaving more room for improvement. Moreover, in contrast to previous studies (Desmond et al., 1996; Hochstenbach et al., 2003; Patel et al., 2003), we only included initially impaired patients in our estimation on the prevalence of cognitive recovery. Finally, we studied patients with a first-ever stroke without pre-existent cognitive or functional problems, and this population probably has a larger potential for cognitive recovery than the stroke population in general (Jorgensen, Nakayama, Reith, Raaschou, & Olsen, 1997).

Taken together, our findings show that cognitive changes after stroke have a highly dynamic course and are suggestive of an adaptive reorganisation of brain function after stroke. It has been argued that the mechanism underlying normal learning is the same mechanism that is implicated in the recovery of function following acquired brain damage, i.e. the so-called Hebbian learning mechanism, which involves experience-dependent dendritic sprouting (Robertson & Murre, 1999). Moreover, there are some indications of neuronal regeneration following brain damage (Eriksson et al., 1998). The location of brain plasticity responsible for cognitive recovery is still unclear however, with evidence of both peri-lesional changes as well as contralateral reorganisation (Calvert et al., 2000; Perani, Vallar, Paulesu, Alberoni, & Fazio, 1993), possibly also depending on the interval post-stroke and on the nature of the cognitive deficit.

Several factors emerged as important predictors of domain-specific cognitive recovery, with some factors associated with recovery in multiple cognitive domains and some factors associated with recovery in isolated cognitive domains. A high level of pre-existent ability was an excellent predictor of a good recovery in almost all cognitive domains. One plausible reason is that these patients are more capable of creating a suitable compensation strategy to circumvent their cognitive deficit.

Moreover, it has been suggested that factors such as intelligence or education provide the brain with a 'cognitive reserve capacity' (Staff, Murray, Deary, & Whalley, 2004). The concept of cognitive reserve posits that individual differences in how tasks are processed might provide a differential reserve against brain pathology or age-related changes (Stern et al., 2003). The neurobiological correlates of this 'cognitive reserve' are still uncertain, but animal studies have demonstrated that exposure to a more stimulating environment is associated with a greater synaptic density and more complex neuronal connections (Kolb, 1999). According to this view, a denser connectivity implies more opportunity for cognitive recovery (e.g. Robertson & Murre, 1999; Kolb, 1999). A younger age was also associated with a better recovery in executive functioning, language, and visual and verbal memory. According to the aforementioned view, age reduces the neuronal connectivity and might therefore result in a worse cognitive recovery after brain damage (Robertson & Murre, 1999). Sex did not influence recovery in any of the cognitive domains in our study.

Several lesion locations were related to recovery in cognitive functioning. A lesion involving the frontal lobe was related to poorer recovery in visual perception and construction. Occipital lesions compromised recovery in visual perception and visual memory, probably related to the presence of visual field defects in these patients. Temporal lesions compromised recovery in executive functioning and verbal memory. With respect to memory, the temporal cortex is believed to be responsible for the consolidation of memory traces (Miyashita, 2004), which may explain the association we found with a poorer recovery in verbal memory. In contrast to previous studies that have reported conflicting findings with evidence of both a left and a right hemisphere advantage related to cognitive recovery (Desmond et al., 1996; Hochstenbach et al., 2003), lesion side was not a predictor of recovery in the present study. Lesion volume emerged as an independent predictor of visual memory, but not with respect to recovery in other cognitive functions. These findings indicate that lesion volume is not the major determinant of cognitive outcome after stroke. Prior studies have indeed shown severe cognitive impairment in patients with only small but strategically located lesions (Auchus, Chen, Sodagar, Thong, & Sng, 2002; Szirmai, Vastagh, Szombathelyi, & Kamondi, 2002).

Diabetes mellitus was related to recovery in abstract reasoning, but other vascular risk factors were not related to cognitive recovery in any domain. The link between diabetes mellitus and poor recovery in post-stroke cognitive functioning (Desmond et al., 1996) and cognitive functioning in general (Biessels, Van der Heide, Kamal, Bleys, & Gispen, 2002; Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004) has been demonstrated before. Diabetes mellitus has also been identified as a risk factor for vascular dementia (Biessels et al., 2002). In this respect, it has been shown that both

increases and decreases of glucose concentrations may affect cognition. Also, the neuroradiological alterations in patients with diabetes mimic those observed in the ageing brain, and therefore it has been suggested that diabetes causes an acceleration of the ageing process in the brain (Biessels et al., 2002).

Finally, neither stroke severity, as measured with the NIHSS, nor the presence of depressive symptoms at baseline mediated cognitive recovery. In contrast, the severity of unilateral neglect immediately after stroke was related to a poor recovery in visual memory, but this relation disappeared in the multivariate model. It has been hypothesised that unilateral neglect probably arises from a combination of two deficits, i.e. a rightward bias plus a deficit in spatial working memory (i.e. retaining locations already searched) (Husain et al., 2001). Our findings support this view and suggest that even when the lateral bias disappears, the visual memory capacity may still be affected in the longer term.

Some limitations of this study should be addressed. We only had a single follow-up examination between six and ten months after stroke. Although the largest amount of spontaneous recovery will have taken place within this time range, it is possible that we underestimated the prevalence of recovery. Alternatively, the course of cognitive functioning might change after the first six months, as one recent study has shown that 22% of patients with a stroke or TIA demonstrated a decline in cognitive functioning between 3-6 months post-stroke and after one year (Sachdev, Brodaty, Valenzuela, Lorentz, & Koschera, 2004). Therefore, our cohort is in the process of a further follow-up to examine the nature of domain-specific cognitive change in the longer term. As we were interested in associates of cognitive recovery exclusively related to the stroke, we included a selective stroke population without pre-existent cognitive, neurological, or psychiatric deficits. Therefore, these findings cannot directly be generalised to the population with first-ever stroke as a whole.

In sum, identification and characterisation of cognitive impairment in acute stroke provides valuable and specific prognostic information with respect to long-term cognitive functioning. The prognosis of acute higher-level visual disorders was the most favourable. Cognitive recovery after first-ever stroke was associated with age, pre-existent ability, lesion volume, lesion location, and diabetes mellitus.

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# The Association between Cognitive and Emotional Deficits after Stroke

# Chapter 6

## Early Depressive Symptoms after Stroke

### Neuropsychological Correlates & Lesion Characteristics

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**ABSTRACT**

*Objective* To examine the relation between depressive symptoms and specific cognitive functions in patients with a recent stroke, and to examine associations with lesion characteristics.

*Methods* We studied 126 of 183 consecutive patients within three weeks after a first-ever symptomatic stroke (mean interval, 8.3 ± 4.3 days). Presence and severity of depressive symptoms was assessed with the Montgomery Åsberg Depression Rating Scale. Neuropsychological functioning was examined by means of a detailed neuropsychological examination covering six cognitive domains. We included a healthy control group (N=75) to obtain normative data for the neuropsychological examination. Functional impairment was measured with the modified Barthel Index and the modified Rankin Scale. Symptomatic and pre-existent lesion characteristics were determined on CT or MRI.

*Results* Of the included patients, 40% demonstrated mild and 12% moderate to severe depressive symptoms. Severity of depressive symptoms was related to lesion volume ($p=0.008$), functional impairment (all $p<0.004$), and degree of overall cognitive impairment ($p=0.005$). After adjustment for lesion size, a specific neuropsychological profile emerged in patients with moderate to severe depressive symptoms, affecting primarily memory, visual perception, and language (all $p<0.05$). No association was found between severity of depressive symptoms and lesion location, presence of pre-existent lesions (white matter lesions and silent infarcts) and demographic factors (age, education and sex).

*Conclusions* Moderate or severe symptoms of depression in the early stage post-stroke are associated with a specific pattern of cognitive impairment, lesion size, and functional status. We suggest that depressive symptoms early after stroke are, at least in part, a reactive phenomenon secondary to severe cognitive and functional deficits.

## Introduction

In the first weeks following stroke, the reported prevalence of depression varies from 9% to 37% (Astrom, Adolfsson, & Asplund, 1993; Berg, Palomaki, Lehtihalmes, Lonnqvist, & Kaste, 2001; Robinson, Starr, Kubos, & Price, 1983; Shimoda & Robinson, 1999; Whyte & Mulsant, 2002). Given this high prevalence and the negative impact of post-stroke depression (PSD) on case fatality (Whyte & Mulsant, 2002), functional outcome (Astrom et al., 1993; Herrmann, Black, Lawrence, Szekely, & Szalai, 1998; Parikh, Lipsey, Robinson, & Price, 1987), and rehabilitation (Gillen, Tennen, McKee, Gernert-Dott, & Affleck, 2001; Whyte & Mulsant, 2002), several studies have tried to identify patients who are most at risk for developing depression in the early phase after stroke. One of the most debated questions regarding PSD concerns the role of lesion location. Acute depression has been associated with left anterior lesions or lesions in the underlying basal ganglia (Astrom et al., 1993; Herrmann, Bartels, Schumacher, & Wallesch, 1995; Robinson et al., 1983; Robinson, Starr, Lipsey, Rao, & Price, 1984; Shimoda & Robinson, 1999), but more recent studies were unable to replicate these results (Berg et al., 2001; Carson et al., 2000; Gainotti, Azzoni, & Marra, 1999). Lesion size has been associated with early PSD in a single study (Shimoda & Robinson, 1999), but not in others (Astrom et al., 1993; Robinson et al., 1984). Vascular risk factors (Alexopoulos, 2003; Carney et al., 1987), white matter lesions (De Groot et al., 2000; Steffens, Krishnan, Crump, & Burke, 2002; Taylor et al., 2003), and silent infarcts (Fujikawa, Yamawaki, & Touhouda, 1993) have been related to depression in elderly people without a history of stroke, but studies of early depression in stroke patients have not considered these factors.

In contrast, the association between depression and global cognitive deterioration has been extensively demonstrated in stroke patients (Downhill & Robinson, 1994; Murata, Kimura, & Robinson, 2000; Robinson, Bolla-Wilson, Kaplan, Lipsey, & Price, 1986; Robinson et al., 1983). However, information about specific neuropsychological correlates is lacking. To date, only one study has reported a specific association between poor verbal abilities and depression in the first weeks post-stroke (Berg et al., 2001). Conceivably, other cognitive impairments could also be detected with a more detailed neuropsychological examination.

The aim of the present study was to characterise the neuropsychological profile of patients with depressive symptoms in the early phase of stroke and to examine the relation with characteristics of the acute brain lesion and the presence of older ischaemic lesions.

## METHODS

### PATIENTS

The study population consisted of 183 consecutive patients with first-ever symptomatic stroke admitted to stroke units of three hospitals in the Netherlands (University Medical Centre Utrecht, Tweesteden Hospital Tilburg, St.-Elisabeth Hospital Tilburg) between February 2002 and January 2003. Only patients with a first-ever symptomatic ischaemic stroke or primary intracerebral haemorrhage were included. Diagnosis of stroke was based on both the presence of acute neurological symptoms and a compatible lesion on CT or MRI scan. In order to minimise the influence of pre-existent impairments on cognitive performance, we excluded patients with previous depression, history of alcoholism or drug abuse, pre-existent dependence in activities of daily living (ADL), pre-existent cognitive decline (as defined by a score of 3.6 or higher on the short Informant Questionnaire on Cognitive Decline in the Elderly – IQCODE Dutch Version) (De Jonghe, Schmand, Ooms, & Ribbe, 1997), patients older than 85 years, and patients who refused participation. Taken together, this exclusion procedure resulted in a baseline population of 148 patients. Since we were interested in symptoms of depression in the early phase after stroke, we included only those patients who could be examined within 21 days post-stroke. Consequently, the eventual study population comprised 126 patients with a first-ever symptomatic stroke due to the exclusion of patients with severe disturbances in consciousness and patients unable to communicate because of global aphasia lasting longer than 21 days.

### CONTROLS

A healthy control group was studied (N = 87) to obtain normative data for the neuropsychological examination. Control subjects with signs of depression (either MADRS≥7 or a history of depression), pre-existent cognitive decline (as defined by a score of 3.6 or higher on the short Informant Questionnaire on Cognitive Decline in the Elderly – IQCODE Dutch Version) (De Jonghe et al., 1997), or a history of neurological illnesses were excluded from this study. This resulted in a population of 75 healthy controls. The control group was closely matched to the patient group with respect to age, sex and education. The controls were either spouses or family of patients, or volunteers who came to our attention through advertising in newspapers or by word of mouth.

The Ethics Committee of each participating hospital approved the study protocol. Written informed consent was obtained from each subject.

### Clinical assessment

Presence and severity of depressive symptoms was rated by means of the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979). This observer-rated scale is a 10-item scale ranging from 0-60 and puts little emphasis on somatic symptoms. Therefore, it has often been used in elderly patients and patients with stroke (Singh et al., 2000; Suenkeler et al., 2002; Wiart, Petit, Joseph, Mazaux, & Barat, 2000).

All patients received a detailed neuropsychological examination covering the six major cognitive domains. Each domain was composed of at least two neuropsychological tasks resulting in the following test battery (Lezak, Howieson, & Loring, 2004): (1) *reasoning* [Raven Advanced Progressive Matrices (short form) and Similarities (WAIS-III)], (2) *memory* [Rey Auditory Verbal Learning Test and Rey-Osterrieth Complex Figure-delay], (3) *executive functioning* [Brixton Spatial Anticipation Test, Visual Elevator (Test of Everyday Attention) (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994), and Letter Fluency], (4) *visuo-perception and construction* [Judgement of Line Orientation (short form), Test of Facial Recognition (short form), Rey-Osterrieth Complex Figure–copy,], (5) *attention* [Digit Span (WAIS-III), Corsi Block Span, Star Cancellation (Behavioural Inattention Test)], (6) *language* [Token Test (short form) and Boston Naming Test (short form)]. We used the number of impaired cognitive domains (0-6) to represent overall cognitive performance.

Functional status was evaluated with the modified Barthel Index (Mahoney & Barthel, 1965). This is a commonly used basic ADL checklist ranging from 0 (completely dependent) to 20 (completely independent). Handicap was rated with the modified Rankin Scale (Van Swieten, Koudstaal, Visser, Schouten, & Van Gijn, 1988) ranging from 0 (no symptoms) to 5 (severe disability). Both functional measurements were performed on the same day as the neuropsychological examination.

### Neuro-imaging

Lesion characteristics were determined from CT (N=65) or MRI (N = 61) by an experienced stroke neurologist (HBvdW) who was blind for the clinical data. Lesions were classified by territory of arterial blood supply (classified as anterior, middle, posterior, vertebral, or basilar artery), and involvement of supra- (left, right, bilateral) or infratentorial (brain stem or cerebellum) areas. Supratentorial stroke lesions were further dichotomised into (1) purely subcortical and (2) combined cortical and subcortical lesions. Moreover, involvement of the caudate nucleus, internal capsule, basal ganglia and thalamus was rated as absent or present. Silent infarcts were classified as present when an infarct was found in the brain, without the description by

the patient, family or medical record of a prior stroke event. The extent of white matter lesions was classified as follows: 0 = no white matter lesions 1 = minor white matter lesions 2 = moderate white matter lesions 3 = confluent white matter lesions (Van Swieten, Hijdra, Koudstaal, & Van Gijn, 1990). Lesion volume was calculated with Leica Q500 MCP image analysis software by manual tracing of the lesion on each slice showing the infarct or haemorrhage. This method has been shown to have a high inter-rater reliability and is described in detail elsewhere (Van der Worp et al., 2001).

### STATISTICAL ANALYSES

Patients were classified into three categories based on the level of depressive symptoms (absent, mild, moderate to severe) according to standardised cut-off scores on the MADRS (Snaith, Harrop, Newby, & Teale, 1986). Between-group comparisons were made by using chi square analyses for nominal data, Kruskall Wallis-H tests for ordinal data and univariate analyses of variance (ANOVA) for continuous data. Post-hoc Scheffé comparison tests were undertaken for further analysis of significant ANOVA´s.

Patients' neuropsychological test results were standardised into z-scores based on the means and standard deviations of the control group. It should be noted that no difference was found between spouses or family of patients and the community volunteers in our control sample with respect to cognitive function. Performance was categorised as cognitive impairment if z-scores of patients fell below -1.65 (Lezak et al., 2004). Domain scores were calculated by averaging z-scores of tasks contributing to the specific domains, and compared between patient groups. All tests were two-tailed with results considered significant at $p<0.05$.

## RESULTS

Of the patients included, 48% had no depressive symptoms (MADRS < 7), 40% had mild depressive symptoms (MADRS 7-19), and 12% had moderate to severe depressive symptoms (MADRS > 19). Patients' demographic and functional characteristics are presented in Table 1. The three groups did not differ with respect to age, education, sex or days between stroke onset and the examination. Patients with moderate to severe depressive symptoms were more physically dependent and had a more severe handicap than patients with no or mild depressive symptoms. During their hospital stay, 10 of 126 (8%) patients received antidepressant medication. Three of these patients demonstrated no depressive symptoms on the MADRS, 5 patients showed mild symptoms and 3 patients showed moderate to severe symptoms.

TABLE 1. Patients' characteristics classified by severity of depressive symptoms.

| | Overall | Severity of depressive symptoms | | | |
|---|---|---|---|---|---|
| | | Absent | Mild | Mod./Sev. | p |
| | n = 126 | n = 60 | n = 51 | n = 15 | |
| Age, mean (sd) | 62.3 (13.3) | 61.9 (12.5) | 62.0 (14.7) | 65.1 (11.9) | 0.70 † |
| Education, median (range)§ | 4.0 (1-7) | 4.0 (1-7) | 4.0 (1-7) | 4.0 (2-6) | 0.47 * |
| Male sex, % | 46.8 | 48.3 | 49.0 | 33.3 | 0.54 ‡ |
| Interval (days) stroke to examination, mean (sd) | 8.3 (4.3) | 7.8 (4.4) | 8.7 (4.6) | 8.9 (2.7) | 0.46 † |
| Modified Barthel Index, median (range) | 17.0 (2-20) | 18.0 (5-20) | 18.0 (2-20) | 9.0 (2-18) | 0.003 * |
| Modified Rankin Scale, median (range) | 3.0 (1-5) | 3.0 (1-4) | 2.0 (1-5) | 4.0 (2-5) | 0.004 * |

sd = standard deviation; Mod./Sev. = moderate to severe * by Kruskall Wallis test. † by univariate ANOVA. ‡ by $\chi^2$ test. § Education level is scored using 7 categories (1= not finished primary school; 7 = university degree (Hochstenbach, Den Otter, & Mulder, 2003).

Lesion characteristics were similar in patients investigated by CT or MRI. Therefore, further analysis was carried out on the group as a whole. Table 2 shows an overview of lesion characteristics for the entire group and for each of the three categories of depressive symptoms.

TABLE 2. Lesion characteristics classified by severity of depressive symptoms.

| | Overall | Severity of depressive symptoms | | |
|---|---|---|---|---|
| | | None | Mild | Moderate to severe |
| | n=126 | n=60 | n=51 | n=15 |
| Type of stroke | | | | |
| Infarct | 88.1 | 91.7 | 82.4 | 93.3 |
| Haemorrhage | 11.9 | 8.3 | 17.6 | 6.7 |
| Lesion location | | | | |
| Supratentorial | | | | |
| Left | 42.1 | 46.7 | 37.3 | 40.0 |
| Right | 39.7 | 28.3 | 51.0 | 46.7 |
| Bilateral | 3.2 | 5.0 | 2.0 | 0 |
| Infratentorial | | | | |
| Brain stem | 7.1 | 10.0 | 5.9 | 0 |
| Cerebellum | 7.9 | 10.0 | 3.9 | 13.3 |
| Supratentorial lesions | | | | |
| Cortical/subcortical | 45.8 | 37.5 | 47.8 | 69.2 |
| Subcortical | 30.8 | 62.5 | 52.2 | 30.8 |
| Vascular territory | | | | |
| Anterior cerebral artery | 2.4 | 1.7 | 2.0 | 6.7 |
| Middle cerebral artery | 61.1 | 63.3 | 65.9 | 66.7 |
| Posterior cerebral artery. | 20.6 | 13.3 | 31.4 | 13.3 |
| Vertebral artery | 8.7 | 11.7 | 3.9 | 13.3 |
| Basilar artery | 7.1 | 10.0 | 5.9 | 0 |
| Lesion volume*, $cm^3$ | 16.5 ± 27.3 | 11.6 ± 24.7 | 16.7 ± 27.5 | 35.8 ± 29.7 |
| Silent infarction(s) | 19.8 | 26.7 | 15.7 | 6.7 |
| White matter lesions | | | | |
| Absent | 76.2 | 71.7 | 78.4 | 86.7 |
| Mild | 13.5 | 18.3 | 7.8 | 13.3 |
| Moderate | 7.9 | 6.7 | 11.8 | 0 |
| Confluent | 2.4 | 3.3 | 2.0 | 0 |

Values are within-group percentages, and means ± standard deviations. * $p<0.01$.

A large main effect of lesion volume on severity of depressive symptoms was found between groups [$F(2,124)=5.062$, $p=0.008$]. Post-hoc Scheffé analysis revealed that patients with moderate to severe depressive symptoms had a larger lesion volume than patients with no depressive symptoms ($p=0.008$) or patients with mild depressive symptoms ($p=0.05$). No association could be demonstrated between severity of depressive symptoms and lesion location, territory of arterial blood supply, presence

of silent infarct(s) and extent of white matter lesions. No differences between groups were found in involvement of subcortical structures (Table 3).

TABLE 3. Involvement of subcortical structures classified by severity of depressive symptoms.

| | | Severity of depressive symptoms | | |
|---|---|---|---|---|
| | Overall n=126 | None n=60 | Mild n=51 | Moderate to severe n=15 |
| Caudate nucleus | 8.7 | 6.7 | 9.8 | 13.3 |
| Basal ganglia | 21.4 | 16.7 | 23.5 | 33.3 |
| Thalamus | 13.5 | 11.7 | 15.7 | 13.3 |
| Internal capsule | 27.0 | 23.3 | 29.4 | 33.3 |

Values are within-group percentages.

A significant relationship was found between the severity of depressive symptoms and overall cognitive function, i.e. patients with moderate to severe depressive symptoms demonstrated three times more cognitive impairments than patients with no or mild depressive symptoms [$\chi 2$ (2)=10.4; p=0.005]. Subsequently, we assessed whether differences in neuropsychological profiles could be demonstrated between groups. An ANCOVA was performed to correct for the difference in lesion size between groups. Figure 1 shows mean cognitive domain scores for each group. Between-group differences were found in memory [F (2,122)=4.08; p=0.019], visual perception and construction [F (2,122)=4.64; p=0.012], and language [F (2,122)=3.26; p=0.042]. Further analyses indicated that patients with moderate or severe depressive symptoms performed significantly worse than the other patient groups ($p<0.05$). Patients with mild depressive symptoms showed the same performance as patients without depressive symptoms on all cognitive domains (all $p>0.05$).

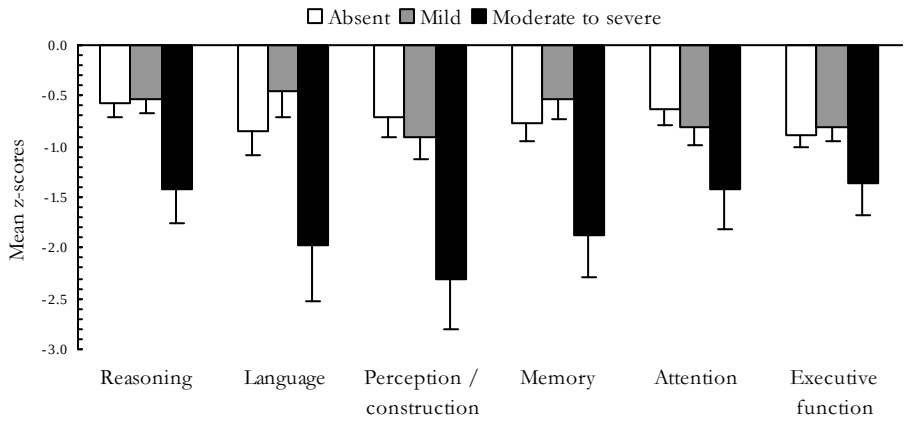


FIGURE 1. Mean z-scores in each cognitive domain across patient groups. Error bars indicate standard errors.

## DISCUSSION

In the present study, we have demonstrated for the first time that stroke patients with early depressive symptoms show a specific neuropsychological profile, which is in contrast with earlier reports of a global cognitive deterioration (Downhill & Robinson, 1994; Kauhanen et al., 1999; Murata et al., 2000; Robinson et al., 1983). Visual perception and construction, memory, and language were particularly affected in patients with moderate to severe depressive symptoms. Age, education, nor sex could account for these findings since these variables were not related to severity of depressive symptoms. Moreover, this pattern emerged after adjustment for the volume of the lesion. The most probable explanation for the selective neuropsychological profile in our patient sample is that aphasia, amnesia and perceptual distortions are immediately apparent and disabling to patients in the early phase of stroke, and that the depressive symptoms are secondary to these impairments. In contrast, impairments in executive functioning, reasoning and attention span are less noticeable in a structured environment like the stroke unit. Alternatively, depression might evolve simultaneously with cognitive impairment following acute stroke. However, given the diverse nature of the cognitive impairments associated with depression severity in our study and the lack of a relationship with lesion location, this explanation seems less likely.

It has recently been suggested that the time elapsed since stroke onset is very important in distinguishing between directly related (biological) and reactive (psychological) forms of PSD (Shimoda & Robinson, 1999). Several studies have reported an association between depression and lesion characteristics in the very early

phase post-stroke, thus supporting the concept of biological depression (Astrom et al., 1993; Herrmann et al., 1995; Robinson et al., 1983; Robinson et al., 1984; Shimoda & Robinson, 1999). More recent studies were not able to replicate these findings (Berg et al., 2001; Carson et al., 2000; Gainotti et al., 1999), for which reason some argue that PSD is always reactive in nature, independent of the interval since stroke onset (Gainotti et al., 1999; Gainotti et al., 1997; Gainotti & Marra, 2002). This view is corroborated by a recent study demonstrating that depressive symptom profiles of patients with PSD in both acute and more chronic stages showed a psychological 'reactive' pattern, whereas depressed patients without a history of stroke demonstrated more biologically determined symptoms (Gainotti et al., 1999).

The present study sheds new light on this ongoing controversy. Neither lesion side nor lesion location was related to severity of depressive symptoms in the early phase of stroke. Furthermore, no association could be demonstrated with involvement of subcortical structures in the brain. The volume of the lesion was the only lesion characteristic associated with the severity of depressive symptoms in the first weeks post-stroke. The neuropsychological profile found in the present study is different from what is usually reported in depressed patients without a history of stroke. Major depression in these patients typically results in impairments in concentration, memory encoding, psychomotor speed, and executive functioning (Elderkin-Thompson et al., 2003; Veiel, 1997), whereas our patients showed disproportionately poor language capacities, long-term memory failure and perceptual distortions. This dissimilar pattern suggests that the underlying mechanisms of cognitive disorders in PSD and major (not stroke related) depression are different. Furthermore, in patients with major depression without a history of stroke, depression has been associated with white matter lesions (De Groot et al., 2000; Steffens et al., 2002; Taylor et al., 2003), silent infarcts (Fujikawa et al., 1993), and cardiovascular risk factors (Alexopoulos, 2003; Carney et al., 1987). In contrast, our study shows that neither silent infarcts nor white matter lesions contribute to depressive symptoms in the early phase post-stroke. Similarly, another study found that the extent of white matter lesions was unrelated to depression at more chronic stages post-stroke (Vataja et al., 2001). Altogether, these findings imply that depressive symptoms occurring in the early phase post-stroke are, at least in part, a reactive manifestation to sudden and severe cognitive and functional impairment, rather than a direct result of damage to specific brain regions.

Our study has the following strengths. First, this study has included a substantial number of patients and it is among the few that examined patients in the very early phase post-stroke. Second, instead of using a global cognitive screening instrument such as the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) or the R-CAMCOG (De Koning, Dippel, van Kooten, & Koudstaal, 2000), we examined

patients with a detailed neuropsychological examination, which allowed evaluation of specific cognitive performance. Third, we chose to assess severity of depressive symptoms with the MADRS, an observer-rated measure that is easy to use in clinical practice, whereas a formal psychiatric assessment might not be feasible in some patients with cognitive or aphasic disturbances. Moreover, the MADRS has often been used in stroke patients (Singh et al., 2000; Suenkeler et al., 2002; Wiart et al., 2000) and puts little emphasis on somatic symptoms. This is important since some of the symptoms that are used to diagnose depression such as fatigue, pain, or sleeping disorders, can be the direct result of the stroke itself (Gainotti et al., 1997). Given that these somatic symptoms are common in the first weeks of stroke, we avoided categorising patients by means of standard self-rating questionnaires or standard criteria.

Several limitations of our study should also be addressed. First, in order to maximise comparability between CT and MRI, simple methods for rating white matter lesions and silent infarcts were used. These methods are less detailed than volumetric methods. Moreover, given that the extent of subcortical but not periventricular white matter lesions has been related to depression in patients without a history of stroke (De Groot et al., 2000), the location of white matter changes and silent infarcts might still be important in stroke patients. Second, in order to study neuropsychological correlates of early depressive symptoms and the relation with lesion characteristics, we excluded patients with pre-existent cognitive dysfunction or depression. Presumably, these patients show more white matter lesions and silent infarcts than our patient population. Third, since we were interested in the acute phase post-stroke, patients with global aphasia and with severe disturbances of consciousness could not be included in this study.

In conclusion, the present study is the first to examine the relation between severity of depressive symptoms and detailed neuropsychological functioning in the very early phase after stroke. The presence of severe depressive symptoms in this early stage is associated with specific cognitive impairment, large lesion size, and poor functional status. These findings might contribute to the early identification of patients at risk for developing depression. We suggest that early depressive symptoms in stroke patients are, at least in part, a reactive phenomenon secondary to severe cognitive and functional deficits.

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# Chapter 7

## Early Cognitive Impairment Predicts Long-term Depressive Symptoms and a Reduced Quality of Life after Stroke

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**ABSTRACT**

*Background and purpose* The aim of the present study was to examine cognitive impairment in the early phase post-stroke as a risk factor for long-term depressive symptoms (DS) and reduced quality of life (QOL).

*Methods* We evaluated 143 patients within the first three weeks after first-ever stroke. Predictor variables included cognitive impairment as assessed with an extensive neuropsychological examination covering 7 distinct cognitive domains, demographic data, vascular risk factors, lesion characteristics, and clinical factors at admission. Independent predictor variables associated with DS (Montgomery Ásberg Depression Rating Scale ≥7) and QOL (Stroke-Specific Quality of Life Scale) were identified with multiple logistic and linear regression.

*Results* DS after six months were independently associated with cognitive impairment at baseline (odds ratio (O.R.)=3.4; 95% confidence interval (CI)=1.2-9.7), DS at baseline (O.R.=3.3; 95%CI=1.1-9.7), female sex (O.R.=4.4; 95%CI=1.5-13.1), diabetes mellitus (O.R.=10.0; 95%CI=1.5-67.0), and previous TIA(s) (O.R.=6.2; 95%CI=1.0-37.6). Cognitive impairment (beta=-.261; p=0.01), age (beta=-.223; p=0.02), and functional dependence (beta=-.242; p=0.02) were risk factors of a reduced QOL, whereas pre-existent hypercholesterolaemia (beta = 0.194; p=0.05) predicted a higher QOL. Among all cognitive disorders at baseline, unilateral neglect was the greatest risk factor for DS after six months (O.R.=9.5; 95%CI=1.9-48.5), whereas a disorder in visual perception/ construction affected QOL the most (beta=-.44; p<0.001).

*Conclusions* Cognitive impairment in the acute phase after stroke is an independent predictor of long-term DS and low QOL.

## INTRODUCTION

Depression is a common complication after stroke and is associated with increased mortality (Williams, Ghose, & Swindle, 2004), poor functional outcome (Chemerinski, Robinson, & Kosier, 2001), and decreased quality of life (Sturm et al., 2004). Over the past 20 years conflicting findings have been reported regarding the association between cognitive impairment and depressive pathology after stroke. Whereas most studies have reported an association with cognitive impairment (e.g. Kauhanen et al., 1999; Nys et al., 2005a; Verdelho, Henon, Lebert, Pasquier, & Leys, 2004), others did not find such an association (Aben et al., 2002), or were able only to show that this association held in patients with left hemisphere damage (Bolla-Wilson, Robinson, Starkstein, Boston, & Price, 1989; Downhill & Robinson, 1994; Spalletta, Guida, De Angelis, & Caltagirone, 2002). Furthermore, there has been some debate regarding the direction of causality between cognitive impairment and depressive pathology after stroke, with the mainstream of studies claiming that depression causes or exacerbates cognitive impairment after stroke (the so-called pseudo-dementia) (e.g. Kimura, Robinson, & Kosier, 2000; Murata, Kimura, & Robinson, 2000; Narushima, Chan, Kosier, & Robinson, 2003). The majority of these studies have assessed *post-stroke depression* based on the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) and/or using self-rating scales such as the Beck Depression Inventory. However, communication difficulties and severe cognitive impairment may complicate the assessment of depression in patients who recently suffered a stroke. Consequently, the diagnostic approach often has resulted in the exclusion of patients with severe cognitive impairment (e.g. Kauhanen et al., 1999; Rampello et al., 2004). Moreover, it has recently been shown that there is a dissocation between depressive behaviour and the subjective experience of depression, particularly in patients with anosognosia (Carota et al., 2005). This finding might suggest the existence of "an anosognosia for depression" (Carota et al., 2005; Biran & Chatterjee, 2003), which emphasises the importance of administering observational methods in acute stroke patients with cognitive impairment. Although observer-rated scales assessing depressive symptoms do not allow for a diagnosis of depression, they are better equipped to examine the relation between cognitive impairment and depressive pathology after stroke. One recent study demonstrated that the presence of observer-rated depressive symptoms at six months post-stroke is closely related to the presence of dementia at six months (Verdelho et al., 2004). At present, it is still unclear whether cognitive impairment early after stroke is a risk factor of depressive symptoms, independent of other wll-known medical and demographic predictors. Given that a recent clinical trial found that depressed patients with cognitive impairment after

stroke show a resistance to antidepressant medication compared to depressed patients without cognitive impairment (Spalletta & Caltagirone, 2004), it might be particularly important to examine the relative contribution of early cognitive impairment in the prediction of long-term depressive symptoms in more detail.

In addition to emotional and cognitive disturbances, stroke patients frequently report a reduced subjective health perception or 'quality of life' (QOL) (Sturm et al., 2004). In the few studies that examined the relative contribution of cognitive performance in the prediction of QOL after stroke, either no significant association was found (Jonkman, De Weerd, & Vrijens, 1998), or a selective association with aphasia was reported (Kwa, Limburg, & De Haan, 1996). However, none of these studies examined cognitive functioning by means of an extensive neuropsychological examination tapping distinct cognitive functions, while specific cognitive disorders might affect quality of life after stroke differently.

In the present study, we aimed (i) to test whether acute cognitive impairment is an independent risk factor of DS six months after stroke, and (ii) to examine its relation with long-term QOL. Furthermore, we examined which specific cognitive deficits at baseline were associated with DS and a reduced QOL after six months. To this end, we used a sensitive neuropsychological examination covering a broad range of cognitive domains and adjusted for the presence of DS at baseline, demographic characteristics, vascular risk factors, and lesion characteristics.

## METHODS

### SUBJECTS

The patient population in this study was selected from consecutive patients with a first-ever symptomatic stroke admitted to stroke units of three hospitals in the Netherlands (University Medical Centre Utrecht, Tweesteden Hospital Tilburg, St.-Elisabeth Hospital Tilburg) between February 2002 and January 2003. Only patients with a first-ever ischaemic stroke or primary intracerebral haemorrhage were included. Diagnosis of stroke was based on both the presence of acute neurological symptoms and a compatible lesion on CT or MRI scan. Exclusion criteria were: (1) Pre-existing depression or history that might influence outcome, i.e. history of drug abuse, pre-existent dependence in activities of daily living, or pre-existent cognitive decline (as defined by a score of 3.6 or higher on the short Informant Questionnaire on Cognitive Decline in the Elderly – IQCODE Dutch Version) (De Jonghe, Schmand, Ooms, & Ribbe, 1997), (2) patients older than 85 years, and (3) patients who could not be examined within the first 21 days post-stroke due to severe disturbances in

consciousness or inability to comprehend task instructions. Finally, patients who suffered a recurrent stroke or who developed comorbidity that might affect outcome (i.e. cancer, myocardial infarction, CABG, or psychiatric illnesses) between the first and the second examination were excluded from follow-up examination. Figure 1 presents a chart showing the number of patients who were in- and excluded.

A healthy control group (N=75) was included to obtain normative data for the neuropsychological examination. The controls were either spouses or family of patients, or volunteers who came to our attention through advertising in newspapers or by word of mouth. Control subjects were carefully matched to the stroke patients with respect to age and education.

The Ethics Committee of each participating hospital approved the study protocol. Written informed consent was obtained from each subject.

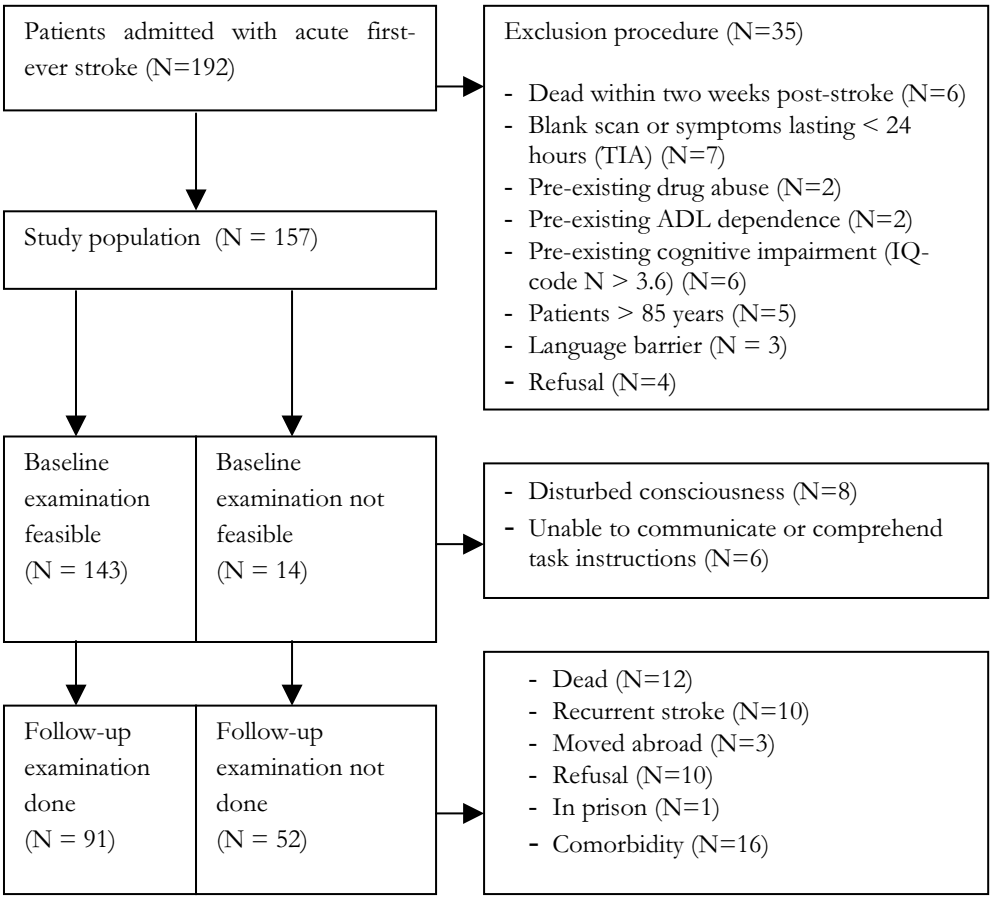


FIGURE 1. Flowchart of patient inclusion.

## PREDICTOR VARIABLES

*Demographic factors*

On admission, we evaluated demographic factors including age (years), level of education (scored with 7 categories ranging from 1:did not finish primary school to 7:university degree, and dichotomised at the median) (Nys et al., 2005b), and sex.

*Vascular risk factors*

Recorded vascular risk factors comprised previously diagnosed and treated diabetes mellitus, hypertension, hypercholesterolaemia, transient ischaemic attack (TIA), smoking during the last five years, alcohol consumption of more than 2 units per day, and a history of cardiovascular disease in a first-degree relative younger than 60 years.

*Clinical scales and neuropsychological assessment*

All clinical variables were assembled within the first three weeks post-stroke (mean interval, 7.8 ± 4.2 days post-stroke). Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989) and categorised as mild if NIHSS ≤ 7 (DeGraba, Hallenbeck, Pettigrew, Dutka, & Kelly, 1999). Functional dependence was assessed with the modified Barthel Index (MBI) (Mahoney & Barthel, 1965) and categorised as present if MBI<19 (Weimar, Ziegler, Konig, & Diener, 2002). Cognitive impairment at baseline was assessed with a neuropsychological examination covering 7 cognitive domains, i.e. abstract reasoning, visual memory, verbal memory, executive functioning, visual perception and construction, language, and unilateral neglect. The neuropsychological test battery is described in detail elsewhere (Nys et al., 2005b). Test scores on individual tasks were transformed into z-scores based on means and standard deviations of the controls. Subsequently, z-scores of tasks belonging to the same cognitive domain were averaged. Patients with disturbances in at least one cognitive domain (z-score < -1.65) were classified as having cognitive impairment at baseline (Nys et al., 2005b). DS severity at baseline was assessed with the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979), and DS were classified as present if MADRS ≥ 7 according to standardised criteria (Snaith, Harrop, Newby, & Teale, 1986). This cut-off value has also been used to indicate the presence of DS in stroke patients (Naess, Nyland, Thomassen, Aarseth, & Myhr, 2005; Verdelho et al., 2004).

*Lesion characteristics*

An experienced stroke neurologist (HBvdW) who was blind to the clinical data determined stroke type and location from CT or MRI. In addition, he recorded the

presence of silent infarcts (Kase et al., 1998) and white matter lesions (scored as present if patients obtained a score > 0 on the 'Van Swieten scale') (Van Swieten, Hijdra, Koudstaal, & Van Gijn, 1990). Lesion volume was calculated by manual tracing of the lesion on each slice showing the infarct or haemorrhage, followed by multiplying the lesion area by the slice thickness in all slices showing the lesion (Van der Worp et al., 2001).

### OUTCOME MEASURES

Follow-up assessment was carried out after a minimum of 6 and a maximum of 10 months, dated from the baseline assessment (mean interval, 7.5 ± 1.3 months). Two distinct types of outcome were used, i.e. long-term DS and QOL. Long-term DS were classified as present if MADRS ≥ 7 at follow-up (Naess et al., 2005; Snaith et al., 1986; Verdelho et al., 2004).

QOL was assessed with the Stroke-Specific Quality of Life Scale (SS-QOL) (Williams, Weinberger, Harris, Clark, & Biller, 1999), which is a disease-specific quality of life measure that consists of 49 items encompassing 12 domains (Social role, Mobility, Energy, Language, Self-care, Mood, Personality, Thinking, Upper Extremity Use, Family Role, Vision, and Work/ Productivity). Each item is ranked on a 5-point Likert scale. The summary score of this scale is an unweighted average of the 12 domains with higher scores indicating better QOL. The summary score was used as the second outcome measure in this study.

### STATISTICAL ANALYSES

First, to determine whether any selection bias had occurred between patients who were re-examined at follow-up and those who were not, we performed Student t-tests for continuous data, Mann-Whitney U tests for ordinal data, and $\chi^2$ analyses for categorical data on the baseline characteristics of patients. Next, we performed a forward stepwise logistic regression analysis with presence of DS in the long term as the dependent variable to determine independent baseline predictors of DS after the first six months. We performed a forward stepwise linear regression analysis with SSQOL as the dependent variable to determine independent baseline predictors of QOL after the first six months. Potential predictors for both analyses were selected from a series of univariate analyses, with a $p \leq 0.1$ level as a screening criterion. Finally, non-parametric Mann-Whitney U tests were performed to examine associations between specific cognitive disorders at baseline and outcome in the long term. Because of the large number of non-parametric analyses, only p-values ≤0.01 were considered significant.

## RESULTS

### POTENTIAL SELECTION BIAS

Of the 143 patients included at baseline, 91 (64%) were re-examined at follow-up. Patients not included at follow-up were significantly older [$t(141) = 2.4$; $p<0.05$], and more of these patients demonstrated white matter lesions [$\chi^2(1) = 7.04$; $p<0.01$] than the included patients. No difference was found with respect to other demographic factors, vascular risk factors, or the prevalence of DS or cognitive impairment at baseline. Characteristics of patients included for follow-up are shown in Table 1. Eleven patients (12%) received antidepressant medication between stroke onset and follow-up.

TABLE 1. Predictors of long-term depressive symptoms: univariate analyses.

| | Entire group | Presence of DS at follow-up | | |
|---|---|---|---|---|
| | N=91 | No DS (N=43) | DS (N=48) | p |
| Demographic characteristics | | | | |
| Age (years), mean ± SD | 61.6 ± 13.2 | 60.8 ± 13.1 | 62.3 ± 13.3 | .57 |
| Female sex | 48.4 | 32.6 | 62.5 | .01* |
| High education‡ | 41.8 | 51.2 | 33.3 | .09* |
| Lesion characteristics | | | | |
| % PICH / all strokes | 7.7 | 4.7 | 10.4 | .30 |
| Lesion location involving | | | | |
| frontal lobe | 13.2 | 7 | 18.8 | .10* |
| parietal lobe | 17.6 | 16.3 | 18.8 | .76 |
| temporal lobe | 19.8 | 18.6 | 20.8 | .79 |
| occipital lobe | 14.3 | 14.0 | 14.6 | .93 |
| striatum | 19.8 | 11.6 | 27.1 | .07* |
| caudate nucleus | 7.7 | 2.3 | 12.5 | .07* |
| thalamus | 11.0 | 9.3 | 12.5 | .63 |
| internal capsule | 25.3 | 25.6 | 25.0 | .95 |
| Lesion volume (ml), mean ± SD | 13.6 ± 22.3 | 8.9 ± 12.8 | 17.7 ± 27.7 | .05* |
| Lesion site | | | | .08* |
| Left supratentorial | 42.5 | 48.8 | 37.0 | |
| Right supratentorial | 43.7 | 31.7 | 54.3 | |
| Infratentorial | 13.8 | 19.5 | 8.7 | |
| Silent infarct(s) | 15.7 | 20.5 | 11.4 | .25 |
| White matter lesions | 15.4 | 16.3 | 14.6 | .82 |
| Vascular risk factors | | | | |
| Hypercholesterolaemia | 17.8 | 20.9 | 14.9 | .45 |
| Hypertension | 41.1 | 44.2 | 38.3 | .57 |
| Diabetes mellitus | 12.2 | 4.7 | 19.1 | .04* |
| Previous TIA(s) | 14.4 | 4.7 | 23.4 | .01* |
| Smoking | 41.1 | 37.2 | 44.7 | .47 |
| Family history | 49.5 | 48.8 | 50.0 | .91 |
| Alcohol > 2 units/ day | 17.8 | 25.6 | 10.6 | .06* |
| Clinical variables in early phase | | | | |
| Cognitive impairment | 41.8 | 25.6 | 56.3 | .01* |
| DS | 49.5 | 34.9 | 62.5 | .01* |
| NIHSS>7 | 25.9 | 18.6 | 29.2 | .24 |
| mBI<19 | 56.0 | 53.5 | 58.3 | .64 |

Values are within-group percentages and means ± standard deviations. Some within-group percentages are based on incomplete samples due to small amounts of missing data. *Variables with p≤0.1 are entered in multivariate analyses. Abbreviations: PICH =primary intracerebral haemorrhage; DS= depressive symptoms; mBI= modified Barthel Index; NIHSS = National Institutes of Health Stroke Scale. ‡High education = 5 (high school education) to 7 (university degree).

### DETERMINANTS OF DS AFTER THE FIRST SIX MONTHS

In the early phase after stroke, 45 patients (49.5%) demonstrated DS, whereas 30 of these patients continued to show DS in the long term. When considering the patient population as a whole, 48 patients (52.7%) demonstrated DS after the first six months. There was no significant difference in the prevalence of DS at baseline and follow-up (McNemars test: p=0.7). Univariate associations between potential predictor variables and DS after the first six months are shown in Table 1. Results of the multiple stepwise logistic regression analysis are summarised in Table 2. At six months, DS were independently associated with cognitive impairment and DS in the acute stage of stroke, female sex, pre-existent diabetes mellitus, and pre-existent TIA(s). Next, we examined which specific cognitive disorders at baseline were associated with DS after six months. Univariate logistic regression analyses adjusted for age, sex, and education showed that patients with unilateral neglect in the first weeks of stroke demonstrated a high risk of showing DS after six months (O.R.=9.5; 95%CI=1.9-48.5), as did patients with visual memory disorders (O.R.=6.8; 95%CI=1.3-35.9), and language impairment (O.R.=4.9; 95%CI=1.2-19.5). With respect to visual perception/ construction, there was a trend towards the development of long-term DS (O.R.=2.7; 95%CI=0.93-7.9). In multiple stepwise analysis, patients with unilateral neglect demonstrated the greatest risk of showing DS after six months (O.R.=9.5; 95%CI=1.9-48.5).

TABLE 2. Predictors of long-term depressive symptoms: stepwise logistic regression analysis.

| Independent baseline predictors | DS at follow-up | |
|---|---|---|
| | O.R. | 95%CI |
| Female sex | 4.41 | 1.5-13.1 |
| Diabetes mellitus | 10.0 | 1.5-67.0 |
| Previous TIA | 6.2 | 1.0-37.6 |
| DS at baseline | 3.3 | 1.1-9.7 |
| Cognitive impairment at baseline | 3.4 | 1.2-9.7 |
| R square | 0.42 | |
| GOF | p=0.29 | |

Values are Odds Ratios (O.R.) and 95% Confidence Intervals (C.I.). Abbreviations: DS=depressive symptoms; GOF = Hosmer and Lemeshow goodness-of-fit.

## DETERMINANTS OF QOL AFTER THE FIRST SIX MONTHS

Univariate associations between potential predictor variables and quality of life after the first six months are shown in Table 3.

TABLE 3. Predictors of long-term QOL: univariate analyses.

| | Standardised B | p-value |
|---|---|---|
| Demographic characteristics | | |
| Age | -.28 | .008* |
| Female sex | -.06 | .58 |
| High education‡ | .29 | .005* |
| Lesion characteristics | | |
| % PICH/all strokes | -.10 | .33 |
| Lesion location involving | | |
| frontal lobe | -.10 | .33 |
| parietal lobe | .12 | .27 |
| temporal lobe | -.07 | .49 |
| occipital lobe | .001 | .99 |
| striatum | -.02 | .89 |
| caudate nucleus | -.10 | .34 |
| thalamus | -.17 | .10 |
| internal capsule | -.22 | .69 |
| Lesion volume | -.22 | .04* |
| Silent infarct(s) | -.05 | .67 |
| White matter lesions | -.04 | .74 |
| Vascular risk factors | | |
| Hypercholesterolaemia | .21 | .04* |
| Hypertension | -.10 | .37 |
| Diabetes mellitus | -.10 | .34 |
| Previous TIA(s) | -.06 | .58 |
| Smoking | .02 | .88 |
| Family history | -.05 | .61 |
| Alcohol > 2 units/ day | .18 | .09* |
| Clinical variables in early phase | | |
| Cognitive impairment | -.39 | .001* |
| DS | -.17 | .11 |
| NIHSS>7 | -.219 | .038* |
| mBI<19 | -.336 | .001* |

*Variables with p≤0.1 are entered in multivariate analyses. Abbreviations: PICH =primary intracerebral haemorrhage; DS= depressive symptoms; mBI= modified Barthel Index; NIHSS = National Institutes of Health Stroke Scale. ‡High education = 5 (high school education) to 7 (university degree).

Four independent predictors of long-term QOL emerged, i.e. early cognitive impairment (beta= -.261; p=0.01), older age (beta= -.223; p=0.02), and ADL dependence in the early phase post-stroke (beta= -.242; p=0.02) predicted a reduced QOL, whereas the presence of hypercholesterolaemia before the stroke predicted a better QOL (beta = 0.194; p=0.05). The R-square in this multivariate model was 0.27.

Among cognitive disorders at baseline, early disorders in executive functioning (beta = -.21; p<0.05), visual perception/ construction (beta = -.47; p<0.001), visual memory (beta = -.37; p<0.001), and unilateral neglect (beta = -.29; p<0.01) were risk factors for a reduced QOL after six months. In multiple stepwise analysis, an impairment in visual perception/ construction was the strongest risk factor of a reduced QOL (beta=-.44; p<0.001). Post-hoc analyses revealed that patients with a deficit in visual perception/construction reported the most complaints in terms of the number of affected SS-QOL domains, followed by patients with unilateral neglect at baseline (Table 4).

TABLE 4. SS-QOL domains affected by specific cognitive deficits.

| | Cognitive deficits at baseline | | | |
|---|---|---|---|---|
| SS-QOL domains | Visual memory | Visual perception/ construction | Unilateral neglect | Executive function |
| Mobility | | X | | |
| Energy | | X | X | |
| Upper extremity | | X | | |
| Work | X | X | X | X |
| Mood | | X | | |
| Self-care | X | X | X | |
| Social relations | | X | | |
| Family relations | | X | X | |
| Vision | | X | | |
| Language | | | | |
| Personality | | X | X | |
| Thinking | | | | |

X indicates Mann-Whitney U tests with p-values ≤ 0.01.

## DISCUSSION

A first important finding of this study is that cognitive impairment in the early phase of stroke is an independent risk factor of DS and a reduced QOL after six months. Until now, acute cognitive impairment after stroke has been studied mainly with

global screening instruments intended to detect dementia, e.g. the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) or the CAMCOG (De Koning et al., 1998). Whereas most studies claim that depression causes cognitive impairment after stroke (Kimura, Robinson, & Kosier, 2000; Murata, Kimura, & Robinson, 2000; Narushima, Chan, Kosier, & Robinson, 2003), the results of our study suggest that early cognitive impairment after stroke aggravates DS in the long term, in addition to other factors. More specifically, patients with unilateral neglect, higher-level visual disorders, and language impairment in the early phase of stroke were at high risk of showing DS in the long term, with acute neglect being the most important cognitive risk factor. Patients with acute higher-level visual disorders and unilateral neglect also reported a reduction in QOL after six months, at the physical level as well as at the mental and social level. Whereas sickness insight in these patients is typically limited in the early phase of stroke, the impact of these impairments apparently becomes clearly visible in the longer term. Therefore, these patients may develop DS as a psychological reaction to the loss of previous capacities. Alternatively, it has been extensively demonstrated that perceptual/ attentional networks in the brain overlap with neural networks involved in mood (Shenal, Harrison, & Demaree, 2003), which may be a more biological explanation why specifically those cognitive disorders seem closely related to DS in our patient sample.

In addition to cognitive impairment, we identified several other independent predictors of DS and QOL after stroke. The presence of DS in the acute stage post-stroke emerged as an independent predictor of DS after six months. This finding is particularly important given the possibility of effective pharmacological treatment of depression in patients with stroke (Robinson, 2003). Moreover, it has been shown that antidepressant treatment is more effective early after stroke as compared to treatment at later stages (Narushima & Robinson, 2003). Antidepressant treatment has been shown to improve functional outcome (Chemerinski et al., 2001) and to decrease mortality after stroke (Jorge, Robinson, Arndt, & Starkstein, 2003). Interestingly, a recent clinical study suggested that depressed stroke patients with comorbid cognitive impairment demonstrated a greater resistance to antidepressant treatment in the long term, but unfortunately this was not a placebo-controlled trial (Spalletta & Caltagirone, 2004). Our study shows that the outcome in cognitively impaired patients is worse, which leaves open the possibility that the treatment effect in the clinical study was comparable in both groups. Future placebo-controlled clinical trials are warranted to evaluate the differential effects of antidepressant treatment in depressed patients with and without cognitive impairment.

Furthermore, two vascular risk factors emerged as independent predictors of DS, namely pre-existent TIA(s) and a history of diabetes mellitus (either type 1 or type 2).

These findings are in line with the 'vascular depression hypothesis' (Alexopoulos et al., 1997), which states that chronic cerebrovascular risk factors predispose to or cause depression. The finding that diabetes mellitus is a risk factor for the presence of depressive pathology after stroke has been reported before, but this association was found solely in patients with a stroke in the left hemisphere (Spalletta et al., 2002). According to some authors, diabetes is a risk factor for DS through a biological mechanism linking the metabolic changes of diabetes to changes in brain structure or function (Jacobson, Samson, Weinger, & Ryan, 2002). Our study also showed that females have a greater risk of showing DS six months after stroke than males, in line with most studies. Similarly, this finding has been consistently reported in subjects without brain damage, but it remains unclear whether the determinants of this sex difference are biological or social (Bebbington, 1998).

In studies testing outcome after stroke it is important to incorporate measures like QOL, as stroke may lead to a broad range of impairments and a wide spectrum of symptom severity. Disease-specific measures, such as the SS-QOL (Williams et al., 1999), may be especially valuable because they are more sensitive than generic measures to meaningful changes in QOL after stroke. Similar to previous work on determinants of QOL (Kwa et al., 1996; Sturm et al., 2004), we found that age and functional dependence were important predictors of a low quality of life. Furthermore, pre-existent hypercholesterolaemia independently predicted a better quality of life after six months. High cholesterol levels in the acute phase of stroke have been associated with a better functional outcome at 1 month post-stroke (Vauthey, de Freitas, van Melle, Devuyst, & Bogousslavsky, 2000). Alternatively, this association may be explained by the use of statins by these patients. Recent studies suggest that the long-term use of statins among patients with coronary artery disease is associated with a reduced risk of depression, anxiety, and hostility (Young-Xu, Chan, Liao, Ravid, & Blatt, 2003). An ongoing trial seeks to ascertain the beneficial or adverse effects of statins on a set of noncardiac endpoints in elderly patients, including cognition, mood, and behaviour (Golomb, Criqui, White, & Dimsdale, 2004).

Several limitations of the present study should be addressed. First, the relatively small number of patients may have resulted in important variables being missed because of multicollinearity or lack of power. Secondly, our models have been tested in the data set from which they have been derived and have not been validated in an independent cohort. Validation of these models in similar patient populations is needed in future research. Thirdly, we did not assess potential emotional confounders such as catastrophic reactions (Carota, Rossetti, Karapanayiotides, & Bogousslavsky, 2001), apathy (Yamagata, Yamaguchi, & Kobayashi, 2004), or anxiety (Leppavuori,

Pohjasvaara, Vataja, Kaste, & Erkinjuntti, 2003), although the presence of these disorders might have affected the MADRS or SSQOL scores to some extent.

In conclusion, cognitive impairment in the first weeks after stroke is an important risk factor of long-term depressive symptoms and a reduced quality of life. Our findings may assist caregivers in the early detection and treatment of patients at risk for adverse outcome after stroke. As there may be differences in the effect of antidepressants in patients with and without cognitive impairment after stroke, future placebo-controlled studies are warranted to compare the effects in patients with and without comorbid cognitive impairment.

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# Neurological Treatment Effects on Cognition

# Chapter 8

# Cognitive and Functional Outcome after Intravenous Recombinant Tissue Plasminogen Activator Treatment in Patients with a First Symptomatic Brain Infarct

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**ABSTRACT**

*Background and purpose* The aim of this study was to examine whether intravenous recombinant tissue plasminogen activator (rt-PA) treatment given in the acute phase of ischaemic stroke has a favourable effect on cognitive and functional outcome at six months post-stroke.

*Methods* The present study included 92 patients with a first-ever symptomatic infarct, of which 25 patients (27%) were subjected to rt-PA treatment in the first three hours post-stroke. Multivariate logistic regression analyses adjusted for stroke severity, education, age, and sex were performed to examine whether rt-PA treatment influenced cognitive outcome (assessed with a neuropsychological examination covering 7 cognitive domains), basic ADL independence (modified Barthel Index ≥19), and instrumental ADL independence (Frenchay Activities Index ≥15) after six months.

*Results* The adjusted odds ratio for intact cognition was 1.0 (95%CI 0.2 to 4.3), that for basic ADL outcome 13.5 (95%CI 1.4 to 129.4) and for instrumental ADL 7.1 (95%CI 1.2 to 42.2).

*Conclusion* Our findings suggest that rt-PA treatment is associated with a favourable basic and instrumental ADL outcome, but not with a beneficial cognitive outcome after six months.

## INTRODUCTION

Patients treated with intravenous recombinant tissue plasminogen activator (rt-PA) within the first three hours after stroke have a favourable clinical outcome at three months post-stroke as compared to patients treated with placebo (The NINDS rt-PA Stroke Study Group, 1995; Hacke et al., 1995). Similar treatment effects have been found after six months and one year post-stroke (Kwiatkowski et al., 1999). The benefit of rt-PA is thought to be due to the early recanalisation of occluded arteries, resulting in increased cerebral reperfusion (Grotta & Alexandrov, 1998) and a subsequent reduction of lesion volume (The NINDS rt-PA Stroke Study Group, 2000). The sooner thrombolytic treatment is administered after stroke, the greater the efficacy of the treatment (Hacke et al., 2004; Marler et al., 2000). Although the majority of studies report a beneficial effect of rt-PA, there are also some reports of adverse effects, such as an increased prevalence of mortality and intracerebral haemorrhage in the first week post-stroke (NINDS, 1995) and neurotoxic effects of rt-PA via potentiation of excitotoxicity when recanalisation after treatment is unsuccessful (Busch et al., 2002).

Cognitive impairment is known to be strongly associated with an adverse functional outcome (Nys et al., 2005) and with post-stroke dementia (Lin et al., 2003). Therefore, it is useful to evaluate whether rt-PA treatment might reduce the prevalence of cognitive impairment after stroke. Moreover, while it has been shown that patients treated with rt-PA have a favourable outcome with respect to basic activities of daily life (bADL) (NINDS, 1995; Hacke et al., 1995; Kwiatkowski et al., 1999), it is unknown whether this also applies to more complex activities that are necessary for independence at home (instrumental ADL: iADL).

The aim of this study was to examine if intravenous rt-PA treatment in the first three hours post-stroke has a beneficial effect on cognitive and functional outcome after six months, independent of demographic factors and stroke severity at baseline.

## METHODS

### PATIENTS

Patients with a first-ever symptomatic ischaemic stroke admitted to stroke units of three hospitals in The Netherlands (University Medical Centre Utrecht, St. Elisabeth Hospital Tilburg, and Tweesteden Hospital Tilburg) between January 2002 and July 2004 were eligible for inclusion in the present study. The diagnosis of stroke was based on the presence of both an acute focal deficit and an associated lesion on CT or

MRI. Patients with a normal scan underwent a second scan within the first week post-stroke. We excluded patients with a neurological or psychiatric history, with a history of pre-existent cognitive deterioration (as defined by a score of 3.6 or higher on the short Informant Questionnaire on Cognitive Decline in the Elderly – IQCODE Dutch Version) (De Jonghe, Schmand, Ooms, & Ribbe, 1997), and patients who were admitted to the hospital > 24 hours following the first symptoms. Patients older than 85 years were also excluded to prevent disproportional aging effects on cognitive performance. We applied no exclusion criteria with regard to the severity of post-stroke cognitive impairment, and both patients with aphasia and unilateral neglect were included. In the University Medical Centre Utrecht, intravenous administration of rt-PA was supplied to all patients arriving at the stroke unit within three hours after stroke, if they did not have exclusion criteria for thrombolysis as recommended in the NINDS study (1995). The other two participating centres (St. Elisabeth & Tweesteden Hospital) did not yet provide rt-PA at the time of data collection. Therefore, we were able to include patients who arrived at the hospital within three hours of stroke onset but who received no treatment with rt-PA. Apart from the rt-PA intervention, stroke treatment was similar in the three centres and standardised according to the same stroke unit protocol. On the whole, 25 patients received thrombolytic treatment and 67 patients did not.

A control group was assembled as a reference sample for the neuropsychological examination, consisting of 75 subjects living in the community. The controls were either spouses or family of patients, or volunteers who came to our attention through advertising in newspapers or by word of mouth. Control subjects were carefully matched to the stroke patients with respect to age, education, and sex.

The ethics committee of the three hospitals approved the study protocol. Informed consent was obtained from all participating subjects before inclusion in the study.

### BASELINE DATA

Stroke severity at the time of admission on the stroke unit was obtained from the medical files by means of the National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989). In addition, demographic factors were recorded, i.e. age, sex, and level of education (scored with 7 categories ranging from 1: did not finish primary school to 7: university degree, and dichotomised at the median) (Nys et al., 2005).

An extensive neuropsychological examination was administered after a minimum of six and a maximum of ten months post-stroke. This examination comprised seven cognitive domains (Lezak, Howieson, & Loring, 2004; Nys et al., 2005): (1) abstract

reasoning [Raven Advanced Progressive Matrices (short form), Similarities (WAIS-III)] (2) verbal memory [Rey Auditory Verbal Learning Test, Wechsler Memory Scale – story recall A, Digit Span (WAIS-III)] (3) executive functioning [Brixton Spatial Anticipation Test, the Visual Elevator (Test of Everyday Attention), Letter Fluency, the Stroop Colour Word test, Zoo test (BADS)] (4) visual perception and construction [Judgment of Line Orientation (short form), the Test of Facial Recognition (short form), WAIS-III block patterns] (5) visual memory [Wechsler Memory Scale-Visual Reproduction, Location Learning Task, Corsi Block Span] (6) language [Token Test (short form), Boston Naming Test (short form), Chapman Reading Task], and (7) unilateral neglect [Star Cancellation]. The procedure of administering multiple neuropsychological tasks within one cognitive domain allowed us to transform raw test scores of patients on individual tasks into compound z-scores based on the means and standard deviations of the control group (Nys et al., 2005). Subsequently, we averaged z-scores of tasks belonging to the same cognitive domain. Cut-off scores for cognitive impairment within each domain were determined by a performance that differed from the control mean at the 0.05 level of significance (z-score $< -1.65$) (Lezak et al., 2004).

### DEFINITION OF OUTCOME MEASURES

Cognitive outcome as assessed with the abovementioned neuropsychological examination was classified as (i) 'cognitively intact' [defined as no impairment on any of the cognitive domains] vs. 'cognitively impaired' [defined as an impairment in at least one cognitive domain] and (ii) severity of cognitive impairment [cognitive compound score which is the unweighted average of the seven cognitive domain scores].

Functional outcome was assessed with two separate ADL measures, that is basic and instrumental ADL measures. Basic ADL instruments assess straightforward activities such as personal hygiene and dressing, whereas instrumental ADL instruments assess more complex activities, such as grocery shopping, household management, and social activities. In this study, basic ADL was determined with the modified Barthel Index (mBI) (Mahoney & Barthel, 1965). An mBI value $\geq 19$ was used as an indication of intact basic ADL function (Weimar, Konig, Kraywinkel, Ziegler, & Diener, 2004). The Frenchay Activities Index (FAI) (Wade, Legh-Smith, & Langton Hewer, 1985) was used to assess instrumental ADL. In total, the scale comprises 15 individual activities summed to give an overall score ranging from 0 (inactive) to 45 (very active). Intact instrumental ADL function was defined as FAI $\geq$ 15 (Wilkinson et al., 1997).

### STATISTICAL ANALYSES

The primary aim of the analyses was to compare the prevalence of intact cognition and basic and instrumental ADL independence after six months between the patients treated with rt-PA and those not treated. To this end we calculated crude and adjusted odds ratios (OR) with corresponding 95% confidence intervals (95% CI) by means of logistic regression. We adjusted for age, sex, level of education, and NIHSS at baseline. In addition we compared the mean cognitive compound score between the patients treated with rt-PA and those not treated by means of linear regression adjusting for the same four factors.

## RESULTS

Patient characteristics are shown in Table 1. In general, patients who received rt-PA treatment demonstrated a more severe stroke.

TABLE 1. Patient characteristics (N=92).

| | No rt-PA (N=67) | rt-PA (N=25) |
|---|---|---|
| Interval stroke onset to examination, months | 7.7 ± 1.4 | 8.0 ± 2.2 |
| Age, years | 61.7 ± 12.7 | 59.9 ± 13.9 |
| High education*, % | 43% | 64% |
| Female sex, % | 43% | 24% |
| NIHSS, median [range] | 5 [2-17] | 11 [2-18] |

Values are means ± standard deviations unless otherwise indicated. *High education = 5 (high school education) to 7 (university degree).

An intact cognitive outcome after six months was present in 52% of patients treated with intravenous rt-PA vs. 66% of patients who were not treated with rt-PA (adjusted OR 1.0; 95% CI 0.2 to 4.3) (Table 2). Basic ADL independence was found in respectively 88% and 82% of patients (adjusted OR 13.5; 95% CI 1.4 to 129.4), and instrumental ADL independence was observed in respectively 83% and 80% (adjusted OR 7.1; 95% CI 1.2 to 42.2). Treatment with rt-PA exerted no positive effect on the severity of cognitive impairment (adjusted difference 0.01; 95% CI –0.4 to 0.6).

TABLE 2. Crude and adjusted relationships of rt-PA treatment with cognition and ADL.

| | Crude relationship | | Adjusted* relationship | |
|---|---|---|---|---|
| Outcome | OR / Beta** | 95% CI | OR / Beta** | 95% CI |
| Intact cognition | 0.57 | 0.22 to 1.44 | 1.00 | 0.23 to 4.33 |
| Cognitive compound score | -0.17 | -0.61 to 0.28 | 0.008 | -0.39 to 0.55 |
| bADL independence | 1.6 | 0.41 to 6.22 | 13.5 | 1.41 to 129.41 |
| iADL independence | 1.3 | 0.37 to 4.38 | 7.09 | 1.19 to 42.17 |

*Adjusted for age, sex, level of education, and NIHSS.

**All data are odds ratios derived from logistic regression, except for the cognitive compound score which are betas derived from linear regression. An odds ratio <1 denotes less patients with intact cognition or ADL independence in the patients treated with rt-PA. Beta indicates the difference in the mean cognitive compound score between the patients treated and not treated with rtPA. Beta < 0 denotes worse cognitive compound scores among the rt-PA treated patients.

## DISCUSSION

This is the first report on cognitive and instrumental ADL outcome after treatment with intravenous rt-PA administered in the first three hours post-stroke. Our findings suggest that rt-PA treatment is associated with a favourable basic and instrumental ADL outcome, but not with a beneficial cognitive outcome after six months. This sample included only patients who survived a first-ever symptomatic stroke. Therefore, these findings cannot be directly generalised to the stroke population as a whole. Furthermore, it was not possible to randomise treatment. Patients did not receive treatment either because they were admitted to one of the two participating centres in Tilburg (The Netherlands), because they were excluded by means of the NINDS criteria for thrombolytic treatment (NINDS, 1995), or because they arrived too late at the hospital (> 3 hours post-stroke). As a result, patients subjected to rt-PA in our study demonstrated more severe strokes than the untreated patients, in line with findings from a previous study in which patients with more severe strokes arrived earlier in the emergency departments than those whose condition was less severe (Hacke et al., 2004). Risk adjustment statistically addresses this heterogeneity and has been shown to reduce bias in treatment effect estimates (Johnston, Connors, Wagner, & Haley, 2004). Nevertheless, there might be some residual confounding that diminishes the estimated effect of treatment in our study. Yet, functional outcome six months after stroke was better in those treated despite greater stroke severity, with respect to both basic and instrumental ADL. This is an important finding suggesting that rt-PA treatment not only affects straightforward activities such as personal hygiene and dressing, but also more complex activities such as grocery shopping and household management. Independence in these activities enables the stroke patient to be discharged home without being too dependent on others. With respect to basic

functional outcome, our findings replicate and extend a previous study on the benefit of rt-PA at 6 and 12 months post-stroke (Kwiatkowski et al., 1999).

In contrast to our findings concerning functional outcome, we could not demonstrate an effect of rt-PA treatment on the prevalence or the severity of cognitive impairment six months after stroke. Three alternative explanations may be given for this finding. *First*, it is possible that treatment with rt-PA does not affect cognitive outcome at six months. This explanation would suggest that reducing the volume of the lesion is not sufficient to ameliorate cognitive functioning in the long term after stroke. Other factors, such as the location of the lesion (Zekry et al., 2003), the volume of hypoperfusion (Hillis et al., 2004), or neuronal metabolic changes (Van Zandvoort, Van der Grond, Kappelle, & De Haan, 2005) have indeed been shown to be equally or more important for cognitive recovery after stroke. Alternatively, it is possible that rt-PA reduces lesion volume resulting in an improvement of focal cognitive functioning, but that, at the same time, rt-PA is neurotoxic (Busch et al., 2002) resulting in a concurrent global cognitive decline in some cases. A *second* explanation for our finding regarding cognitive outcome may be that rt-PA treatment has a short-term influence on cognitive outcome, but that this effect is not sustained at six months. For instance, the rt-PA group may show a better cognitive outcome after one month than patients who are not treated with rt-PA, but this difference might disappear in the long term due to a gradual recovery in untreated patients resulting in the same cognitive outcome after six months. The *third* explanation concerns the design of the study. Perhaps the statistical power was insufficient to demonstrate a positive effect of rt-PA on cognitive outcome, or the effect is masked by the abovementioned residual confounding of baseline differences between the two patient groups. The latter explanation seems less likely given our findings with respect to basic and instrumental functional outcome. Future studies with randomised and larger stroke samples are needed to examine the short- and long-term effects of thrombolytic treatment on cognitive functioning. Moreover, as the treatment is only safe and effective within the first hours post-stroke (Hacke et al., 2004; Marler et al., 2000), a revolution in neurologic services is needed with an emphasis on immediate care. In addition, public education is essential in order to improve knowledge about symptoms of acute stroke.

In sum, our findings suggest that rt-PA treatment influences basic and functional outcome, but not cognitive outcome after six months. The findings should be confirmed in a population more representative of the patients who are typically enrolled in acute stroke trials. In the meantime, the search for appropriate neuropsychological interventions aimed at reducing cognitive impairment after stroke remains crucial.

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# Uncommon Cognitive Disorders in Acute Stroke

# Chapter 9

## The Role of Executive Functioning in Spontaneous Confabulation

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**ABSTRACT**

*Objective* To follow the recovery course of a patient who exhibited an amnesic-confabulatory syndrome in conjunction with severe executive dysfunction in the first week following bithalamic infarction.

*Background* Previous studies have shown that spontaneous confabulation originates from the combination of amnesia and executive dysfunction, and that the degree of confabulation is determined by the degree of executive dysfunction. However, a few studies have also reported a dissociation between spontaneous confabulation and executive dysfunction. Therefore, the role of executive functioning in spontaneous confabulation is presently unclear.

*Method* Clinical examinations, magnetic resonance imaging (MRI), and cognitive and behavioural assessments with a focus on executive functions were conducted within the first week post-stroke and after six months.

*Results* MRI showed a bithalamic infarction involving the territory of the paramedian arteries predominantly affecting the dorsomedial and intralaminar nuclei of the thalami. Disappearance of spontaneous confabulation paralleled a specific recovery in mental flexibility, whereas all other executive components and long-term memory remained severely impaired at six months post-stroke.

*Conclusions* Our case study provides additional evidence that mental flexibility, but not executive functioning in general is a prerequisite for spontaneous confabulation. Direct or indirect functional deactivation of dorsolateral prefrontal cortex may be necessary for the development of spontaneous confabulation.

## INTRODUCTION

The thalamus plays an important role as a relay function which is connected with multiple brain regions such as the prefrontal cortex, the brain stem, the cerebellum, limbic and paralimbic areas, diencephalic areas, and the basal ganglia (Kumral, Evyapan, Balkir, & Kutluhan, 2001; Levasseur et al., 1992). Four arteries are responsible for the blood supply to the thalamus in each hemisphere: (1) the polar artery of Percheron supplies the anterior part of the thalamus, (2) the thalamo-subthalamic paramedian artery supplies the medial structures, (3) the thalamogeniculate artery of Foix and Hillemand supplies the posterior part, and (4) the posterior choroidal arteries supply the ventral regions of the thalamus (Schmahmann, 2003). One single artery may supply thalamic territories on both sides and therefore, bithalamic infarctions can occur (Kumral et al., 2001; Schmahmann, 2003). Patients suffering from acute bithalamic infarction often demonstrate a variety of marked neurological and neuropsychological symptoms depending on which territory of the thalami is involved. Patients with infarctions involving the territory of the paramedian artery typically demonstrate the most severe clinical picture (Kumral et al., 2001; Schmahmann, 2003). Neurological symptoms in these patients include disorders of consciousness, sleep disorders, vertical gaze paresis and convergence disorders, motor weakness and ataxia (Bogousslavsky, Regli, & Uske, 1988). The most prominent neuropsychological disturbances in the first period after the stroke are global amnesia (Bogousslavsky et al., 1988; Hodges & McCarthy, 1993; Kumral et al., 2001; Malamut, Graff-Radford, Chawluk, Grossman, & Gur, 1992; Stuss, Guberman, Nelson, & Larochelle, 1988; Szirmai, Vastagh, Szombathelyi, & Kamondi, 2002) and abulia (Engelborghs, Marien, Pickut, Verstraeten, & De Deyn, 2000; Guberman & Stuss, 1983). Other frequently reported cognitive impairments are confabulations (Chatterjee et al., 1997; Guberman & Stuss, 1983; Stuss et al., 1988), impairments in executive functioning (Eslinger, Warner, Grattan, & Easton, 1991; Van der Werf et al., 2003), verbal reasoning and mild language disturbances (Chatterjee et al., 1997; Stuss et al., 1988). While amnesia and abulia typically remain chronic in these patients, verbal reasoning and language capacities substantially recover in most reported cases (Graff-Radford, Tranel, Van Hoesen, & Brandt, 1990; Malamut et al., 1992; Stuss et al., 1988). Prognosis with respect to confabulations or executive impairments is less clear. Also, the neuropsychological correlates of spontaneous confabulation are still largely debated. Some authors argue that spontaneous confabulation originates from the combination of amnesia and executive dysfunction (Burgess & McNeil, 1999; Hashimoto, Tanaka, & Nakano, 2000; Kapur & Coughlan, 1980). However, there is also evidence of a dissociation between executive functioning and spontaneous

confabulation in amnesic patients (Dalla Barba, 1993; Dalla Barba, Cipolotti, & Denes, 1990; Schnider, 2001; Schnider, Ptak, von Daniken, & Remonda, 2000). An important explanation for these contrasting findings may lay in the fact that 'dysexecutive functioning' is a very general and ill-defined concept. It is considered to be "a product of the coordinated operation of various processes to accomplish a particular goal in a flexible manner" (Funahashi, 2001 p. 147). Several mechanisms or systems responsible for the coordinated operation of these various processes have been proposed, for example the 'executive control system' (Funahashi, 2001; Salthouse & Miles, 2002), the 'central executive' (Baddeley, 2002), the 'executive-attention framework' (Kane & Engle, 2002), or the 'supervisory system' (Shallice, 2002). The functions under this executive control system are called the 'executive functions', which consist of a range of dissociable subcomponents such as planning, response suppression, or mental flexibility (Burgess, Alderman, Evans, Emslie, & Wilson, 1998; Godefroy, 2003; Lezak, Howieson, & Loring, 2004). Tasks tapping these executive functions not only activate prefrontal regions in the brain, but also subcortical structures (e.g. striatal structures and thalamus) and cerebellar areas (Godefroy, 2003). A methodological issue is that up till now, most studies have focused on assessing executive functioning using only a limited number of executive neuropsychological tasks, while subsequently generalising their results to all aspects of executive functioning. To our opinion, it is important to scrutinise the role of the different aspects of executive functioning in relation to confabulation.

Furthermore, in most studies no distinction is made between "spontaneous" confabulations and "provoked" confabulations, which is a dichotomy originally proposed by Kopelman in 1987. However, there have been a number of studies showing a double dissociation between these two types of confabulations (Schnider & Ptak, 1999), indicating that they represent two distinct disorders rather than different degrees of the same disorder as suggested previously (Fischer, Alexander, D'Esposito, & Otto, 1995; Kapur & Coughlan, 1980; Shapiro, Alexander, Gardner, & Mercer, 1981). Spontaneous confabulations are the most striking in appearance and are characterised by the absolute certainty with which they are uttered in conversation. Occasionally, spontaneous confabulators act according to their false beliefs and even though spontaneous confabulations sometimes tend to have a bizarre content, they are mostly based on true events or habits in the past (Fischer et al., 1995). In contrast, provoked confabulations occur more frequently, can be elicited by direct questioning (Burgess & McNeil, 1999), and may reflect a normal response to a faulty memory (Kopelman, 1987). Moreover, they can be can be induced in healthy controls when they are forced to retrieve details from an imprecise memory (Schnider, 2001). To

study the exact relationship between confabulation and executive functioning, it seems therefore important to fractionate these concepts.

In this single case report, we demonstrate a patient with bithalamic infarction in the territory of the paramedian thalamo-subthalamic artery, causing an amnesic-confabulatory syndrome in conjunction with severe executive dysfunction. We followed the course of these neuropsychological deficits over a six-month period.

## Case description

LW is a 46-year-old, left-handed clerk with 16 years of education and an unremarkable medical history. One morning, he did not show up at work. His parents found him at home in a state of total confusion. Subsequently, he was brought to the hospital where he demonstrated a normal consciousness, a disturbed orientation, a severely affected memory, marked perseveration, confabulation, associative thinking, and anosognosia. Besides a slightly ataxic walking pattern, there were no focal neurological deficits. His blood pressure was within normal limits. CT of the brain, EKG, CSF, and laboratory studies aimed at glucose levels, renal function, autoimmune diseases, dyslipidemia and clotting disorders showed no abnormalities. EEG showed marked slow activity predominantly in frontal, prefrontal, and basal temporal areas. At three days post-stroke, MRI revealed a bithalamic infarction in the territory of the paramedian arteries predominantly affecting the dorsomedial and intralaminar nuclei of the thalami; at six months post-stroke, the residual lesion was considerably smaller on the right side than on the left side (Figure 1). Extensive laboratory studies, cardiological screening including a transesophagal echocardiogram, duplex of the carotid arteries, and cerebral angiography revealed no cause for the infarction.

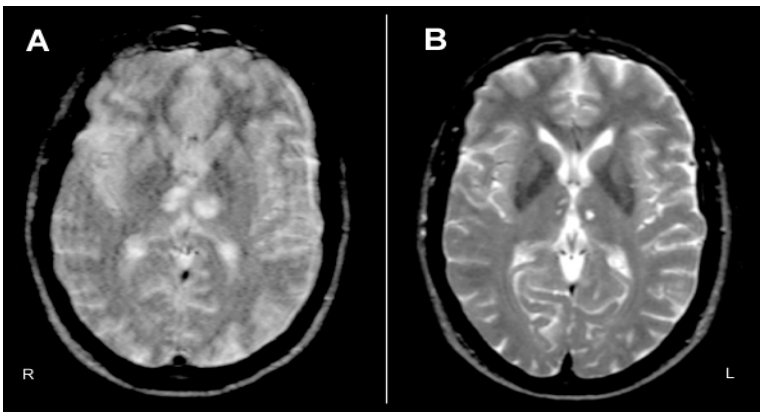


FIGURE 1. Axial T2-weighted MRI showing bilateral thalamic infarction in the paramedian thalamo-subthalamic territory (A) on day 3 post-stroke, (B) at six months post-stroke.

## METHODS

Neuropsychological examination was performed on day 8 and at six months post-stroke (Table 1). The assessments included the following tests (Lezak et al., 2004):
*Estimated premorbid verbal IQ:* measured with the National Adult Reading Test (Dutch Version).
*Working memory:* Non-verbal and verbal working memory were assessed respectively by means of the Corsi Block Span and the WAIS-III Digit Span.
*Memory:* Verbal memory was evaluated by means of the Rey Auditory-Verbal Learning test (Dutch Version), and non-verbal memory by means of the Rey-Osterrieth Complex Figure. Two subtests of the Wechsler Memory Scale-Revised, Logical Memory and Visual Reproduction, were added in the follow-up evaluation.
*Executive functioning*: Four different aspects of executive functioning were evaluated: (1) *resistance to interference* was evaluated by means of the Stroop Color and Word test; (2) *planning abilities* were administered by means of the Zoo test (BADS); (3) *mental flexibility* was administered with two tasks: the Visual Elevator (TEA) (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994) and the Brixton Spatial Anticipation task; (4) *word generation* was measured with Letter Fluency (N and A; each 1 minute).

## RESULTS

Results of both neuropsychological examinations are summarised in Table 1.

TABLE 1. Neuropsychological test results.

| | February 2002 | | August 2002 | |
|---|---|---|---|---|
| Working memory | | | | |
| Digit Span | 7 | impaired | 10 | impaired |
| Corsi Block Span | 5 | average | 5 | average |
| Long term memory | | | | |
| RAVLT | | | | |
| Immediate recall | 7-4-4-3-0 /15 | impaired | 7-7-8-5-6 /15 | borderline |
| Delayed recall | 0/15 | impaired | 0/15 | impaired |
| Passive recognition | 18/30 | impaired | 25/30 | impaired |
| R-O CF | | | | |
| Copy | 35/36 | high average | 36/36 | superior |
| Delayed Recall | 0/36 | impaired | 0/36 | impaired |
| WMS | | ND | | |
| Paragraph recall | | | | |
| Immediate recall | | | 6/22 | impaired |
| Delayed recall | | | 0/22 | impaired |
| Visual reproduction | | ND | | |
| Immediate recall | | | 17/41 | impaired |
| Delayed recall | | | 0/41 | impaired |
| Executive functioning | | | | |
| Response suppression | | | | |
| Stroop Test | 140.5s (3 errors) | impaired | 120.2s (0 errors) | impaired |
| Word generation | | | | |
| Letter Fluency (NA) | 0 | impaired | 5(2+3) | impaired |
| Planning | | | | |
| Zoo Test (BADS) | 0 | impaired | 0 | impaired |
| Mental flexibility | | | | |
| Brixton | 47 errors | impaired | 13 errors | > average |
| Visual Elevator (TEA) | 0/10 | impaired | 9/10 | > average |
| | time/switch | ND | time/switch 4.3 | < average |

ND = not determined. RAVLT = Rey Auditory Verbal Learning Test; R-O CF = Rey-Osterrieth Complex Figure; WMS= Wechsler Memory Scale; BADS = Behavioural Assessment of the Dysexecutive Syndrome; TEA= Test of Everyday Attention.

## EARLY NEUROPSYCHOLOGICAL ASSESSMENT

During his two-month convalescence at the hospital, LW frequently showed both spontaneous and provoked confabulations. In spontaneous conversation, for example, he said he was living in a sect while he was actually living alone. During neuropsychological examination, he thought he was participating in a television quiz

with the neuropsychologist as the quizmaster, and he saw an audience sitting beside the quizmaster, indicating that he showed visual hallucinations congruent with his confabulations. Finally, he often acted on his confabulations (e.g. occasionally he left his bed wandering around the ward, thinking he was working at the hospital as a physician).

LW was disoriented in person, time and place. His premorbid verbal IQ was estimated at 118 (NART). Verbal working memory was impaired, while non-verbal working memory was average. LW demonstrated intact visual fields on confrontation testing, suggesting that his visual hallucinations were not primarily due to visual sensory impairments. In addition, he was unimpaired in visual construction, that is, LW's copy of the Complex Figure of Rey was entirely within normal limits. He suffered from a severe learning deficit with both verbal and visual material. He showed an abnormal learning curve for verbal material, characterized by a steep decrease in performance over trials. On verbal recognition, he reported 3/15 false negatives and 9/15 false positives, indicative of false recognition. He was not able to recall any task, even after a delay of five minutes, which is characteristic of a severe anterograde amnesia. In addition, LW had a retrograde amnesia for information extending up to 5-6 years. He was convinced that he was still in his previous employment and was shocked to hear that family members had died during the last couple of years. Furthermore, he had severe impairments on all components of executive functioning. During the examination he was disinhibited and frequently showed mood swings from euphoria to extreme apathy. He demonstrated severe perseveration during conversation and showed utilization behaviour (e.g. opening all closets when entering the test room, or drawing when a pen was in his surroundings irrespectively of the task he was doing). He demonstrated no insight into his condition. Unless encouraged, he did not initiate any goal-directed activity (abulia).

### Follow-up assessment

At six months post-stroke, the spontaneous confabulations had abated completely. LW still demonstrated confabulations on direct questioning but this time his responses were plausible instead of bizarre. For example, when asked what he had for dinner the day before, he said he made himself a stew at home. In contrast to the marked certainty about the veracity of his answers in the acute phase, he was now more insecure about his responses. His brother indicated that the answer was wrong and that LW always had dinner at his parents' place.

Tests for immediate verbal memory showed a slight improvement. Verbal recognition improved, mainly due to a decrease in false recognition. Retrograde

amnesia was still markedly present, but had shrunken to a period of 2-3 years. Interestingly, a remarkable recovery in executive functioning was found with respect to two tests, the Brixton Spatial Anticipation Test and the Visual Elevator. While the Visual Elevator is a measure of attentional switching (Robertson et al., 1994), the Brixton is a measure of strategic switching and problem-solving (Burgess & Shallice, 1997). Both of these tests have in common that they tap one specific aspect of executive functioning, that is mental flexibility, which is the ability to shift behaviour readily to conform to rapidly changing demands dictated by the environment (Lezak et al., 2004). Apparently, LW now had regained the capacity to shift strategy or set when necessary and he was able to do this at a reasonable speed. However, he was still severely impaired on all other executive components, that is planning, response suppression, and word generation. These impairments were also apparent in his daily behaviour in which he was disorganized, abulic and disinhibited. Although his sickness insight had improved to some extent, he still was not fully aware of his impairments.

## DISCUSSION

Spontaneous confabulation has been reported in a variety of neurological patients, such as patients with bilateral infarction in the territory of the paramedian artery (Bogousslavsky et al., 1988; Chatterjee et al., 1997; Stuss et al., 1988), but also in Wernicke-Korsakoff patients, patients with hypothalamic damage, traumatic brain injury, multiple sclerosis, herpes simplex encephalitis, ruptured anterior communicating artery aneurysms, and dementia (Fischer et al., 1995). These patients typically have in common the presence of both amnesia and executive disorders. Therefore, it has been argued that spontaneous confabulation originates from the combination of amnesia and executive dysfunction (Burgess & McNeil, 1999; Hashimoto et al., 2000; Kapur & Coughlan, 1980), and that the degree of confabulation is determined by the degree of executive dysfunction (Burgess & McNeil, 1999). Nevertheless, a few studies have reported a dissociation between spontaneous confabulation and executive dysfunction (Dalla Barba, 1993; Dalla Barba et al., 1990), or did not find differences in executive performance between spontaneous confabulators and non-confabulators (Schnider, 2001). In these studies, however, executive functioning was not extensively studied and hence it might be that there is a dissociation in executive components that are related to spontaneous confabulation as has been previously suggested (Burgess & McNeil, 1999; Cunningham, Pliskin, Cassisi, Tsang, & Rao, 1997; Papagno & Baddeley, 1997). Based on the pattern of recovery in LW, we want to stress the role of one specific executive component. Disappearance in spontaneous confabulation was accompanied by a

recovery on two executive tasks that have in common that they tap mental flexibility, whereas all the other executive components assessed in this study (that is planning, word generation and response suppression) remained severely impaired at six months post-stroke. These findings suggest that mental flexibility in particular is associated with spontaneous confabulation. Mental flexibility involves flexibly shifting "from one mental state, directed toward a particular reaction tendency, to another" (Konishi et al., 1998 p. 80). More concretely, this ability allows a person to switch to a new strategy when a certain routine strategy has become unproductive. Inflexibility results in perseveration (Godefroy, 2003), in which patients seem magnetically attracted to whatever is in their perceptual field or current thought. The next question is how perseveration and spontaneous confabulation are related to each other. A possible underlying mechanism is that, when irrelevant thoughts or percepts intrude the ongoing reality or an ongoing strategy because of a spatial or temporal contiguity, it becomes impossible for these patients to switch, on the one hand, between realities resulting in confabulation, or, on the other hand, between strategies, resulting in inflexibility. This is, however, a speculative account and this issue awaits further research.

Convergent evidence for the association between mental flexibility and confabulation comes from studies on persistent spontaneous confabulation. Patients showing long-term confabulation typically demonstrate severe impairments in mental flexibility (Mattioli, Miozzo, & Vignolo, 1999; Stuss, Alexander, Lieberman, & Levine, 1978). Moreover, a previous study (Burgess et al., 1998) pointed out that the degree of perseveration as estimated with the Dysexecutive Questionnaire (BADS) (Wilson, Alderman, Burgess, Emslie, & Evans, 1996) loaded on the same factor as the degree of confabulation, which is also suggestive of a close relation between these impairments. Furthermore, a recent group study investigated the clinical course and lesion characteristics of spontaneous confabulators (Schnider et al., 2000). Patients with orbitofrontal and basal forebrain lesions demonstrated the fastest recovery from spontaneous confabulation. Only one patient continued to confabulate for more than three years and his lesion interrupted thalamic connections to dorsolateral prefrontal cortex. This is also the region that has been shown to be critically involved in mental flexibility in a large number of functional imaging studies and lesion studies (e.g. Berman et al., 1995; Konishi et al., 1998; Smith, Taylor, Brammer, & Rubia, 2004). Therefore, direct or indirect functional deactivation of dorsolateral prefrontal cortex might be a prerequisite for the occurrence of spontaneous confabulation in amnesic patients.

LW's initial scan showed fairly extensive bilateral thalamic lesions in the mediodorsal and intralaminar nuclei. A PET study in patients with similar brain

lesions has demonstrated that the severe cognitive impairments in these patients are probably due to hypoperfusion in diffuse bilateral cortical area's through interruption of extensive thalamo-cortical connections, mainly to prefrontal, temporal and posterior parietal regions (Levasseur et al., 1992). Given that subcortical strokes are often followed by a substantial recovery, perhaps due to changes in cortical function (Weiller, Chollet, Friston, Wise, & Frackowiak, 1992) and/or reorganisation of the thalamus itself (Ohara & Lenz, 2001), LW's recovery might have been due to reactivation of prefrontal areas involved in both mental flexibility and spontaneous confabulation. However, additional research with neuro-imaging of hypoperfused regions at the same time as detailed cognitive testing is needed to delineate the exact brain structures involved in spontaneous confabulation.

Finally, we want to report on another interesting and unusual finding. Whereas most patients, including patients with amnesia, typically show an improvement in performance with each subsequent trial, LW showed an unusual verbal learning curve, in which his performance deteriorated over trials. This deficit has only recently been reported by Heilman & Adams (2003), who introduced the term *cognitive impersistence* to refer to this within-session decline of performance. These authors could not find any prior references to this phenomenon. However, Stuss and co-workers have reported on this phenomenon in 1988, where they introduced a patient, RC, who showed the same decline in performance over trials. Interestingly, RC also sustained a bilateral thalamic infarction, similar to our patients' lesion. No ready explanation has been proposed so far for the rapid loss of information in these patients. Further research and case reports are needed to clarify the nature of this disorder.

To conclude, our case study sheds new light on the ongoing controversy about whether or not impairment in executive functioning is required in spontaneous confabulation. It suggests that mental flexibility, but not executive functioning in general, is related to spontaneous confabulation.

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# Chapter 10

# The Physiological Basis of Visual Hallucinations after Damage to the Primary Visual Cortex

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**ABSTRACT**

We used functional magnetic resonance imaging to examine the neuro-anatomical correlates of visual hallucinations in a hemianopic patient who suffered from bilateral occipital infarction. By cross-correlating the fMRI data with the hallucination events, we were able to identify the cerebral activity underlying the hallucinations. Bilateral activation was observed in the calcarine fissure and medially in the left and right occipital cortex adjacent to the infarcted areas. This pattern of perilesional visual cortex activation during hallucination is consistent with the proposed mechanisms of either a release of inhibition in the visual cortex, or an irritation of tissue in the vicinity of the lesion.

## INTRODUCTION

Hallucinatory experiences are found in a broad range of psychiatric patients, neurological patients, and even in healthy subjects (Aleman & De Haan, 1998). In psychiatric populations, hallucinations are often in the auditory domain and most florid during the acute phase, although visual hallucinations are not uncommon (Bracha, Wolkowitz, Lohr, Karson, & Bigilow, 1989). There is now a growing body of evidence suggesting that the cognitive basis for hallucinations in schizophrenia is related to dysfunction of the perceptual system, mental imagery and reality monitoring, although the precise interactions between these processes remain unclear (Aleman, De Haan, Böcker, Hijman, & Kahn, 2003; Aleman, De Haan, Böcker, Hijman, & Kahn, 2002; Böcker, Hijman, Kahn, & De Haan, 2000). In addition, evidence is accumulating regarding the neuro-anatomical basis of hallucinations in psychiatric populations. It appears that the cortical areas that are involved in the complex processing of incoming perceptual information are also activated during hallucinations in psychiatric populations. For instance, a PET study demonstrated left fronto-temporal lobe activation during auditory hallucinations in schizophrenic patients (Lawrie, Buechel, Whalley, Frith, Friston, & Johnstone, 2002). In a similar vein, an fMRI study demonstrated activation in the supplementary somatosensory area in the parietal lobe during painful hallucinations in a schizophrenic patient (Bar, Gaser, Nenadic, & Sauer, 2002).

In neurology, visual hallucinations appear to be the rule. The most prominent neurological conditions involving visual hallucinations are Lewy body dementia (e.g. McShane, Geding, Reading, McDonald, Esiri, & Hope, 1995), Parkinson's disease (e.g. Bodis-Wolner, 1990), Charles Bonnet Syndrome in patients who are blind (e.g. Schultz & Melzack, 1991), occipital epilepsy (e.g. Panayiotopoulos, 1999), and "peduncular hallucinosis" after brain stem and/ or thalamic lesions (e.g. Feinberg & Rapcsak, 1989). These hallucinations vary widely in content and complexity. Some patients experience the perception of simple shapes and colours (often moving), others perceive distorted complex images (e.g. small people or dwarfs), and still others experience full-blown images of complex scenes (Braun et al., 2003). The different diseases associated with hallucinations seem to indicate that subcortical lesions play a central role in visual hallucinations. However, as Manford and Andermann (1998) argue convincingly in their extensive review of visual hallucinations, there is ample evidence for cortical involvement, especially in the case of complex hallucinations.

In hemianopic patients, hallucinations are frequently localised to the affected part of the visual field (Lance, 1976; Vaphiades, Celesia, & Brigell, 1996; Bar, Gaser, Nenadic, & Sauer, 2002). In addition, hallucinations may be incomplete due to visual

field defects, as reported in a patient whose hallucinations consisted of the lower half of human figures that were limited to the borders of his quadrantanopic field defect (Vogeley & Curio, 1998). In a pilot study in our department with an unselected sample of 40 stroke patients with visual field defects, about one-third admitted to having experienced hallucinations, ranging from simple shapes to complex scenes and objects (Nys, Van Zandvoort, Kappelle, & De Haan, in preparation). Usually, there is a latent period before onset of the hallucinations, and in most cases these experiences dissipate with time (Manford & Andermann, 1998). The reason that patients do often not report visual hallucinations is not caused by a lack of insight as these patients are usually very aware of the fact that their hallucinations are fictitious, but probably lies in the popular association with mental disease. It is likely that in general clinical practice most cases are missed.

In this study, we were interested in the neuro-anatomical correlates of hallucinations after damage to the primary visual areas. To this end, we studied a single hemianopic patient who suffered very frequent hallucinations after stroke. Structural damage was assessed by means of a standard MRI protocol and cortical activation of specific regions of interest (ROI) was assessed by fMRI. It has been shown that the lesions causing hallucinations are significantly smaller that those that cause a hemianopia without any hallucinations (Vaphiades et al., 1996). This suggests that some intact cortex involved with primary visual processing is required to express hallucinations (Manford & Andermann, 1998). Our working hypothesis, based on the existing literature, was that areas in the primary cortical visual areas – close to the lesion that caused the visual field defect – are involved.

## Method

### Case report

RZ, a 66-year-old right-handed man, had an unremarkable medical history apart from diabetes mellitus type 2. In September 2001, he complained to his wife about loss of vision, a weakness in the left leg and later on also in the right leg. In addition, he experienced memory problems. His symptoms were gradually worsening and resulted in hospital admission approximately three weeks following the first symptoms. An MRI scan revealed a bilateral occipital infarction (Figure 1), of which the left-sided infarction was presumably of an older date than the right-sided infarction. Prior to the stroke episode, the patient frequently had experienced migraine attacks accompanied by visual auras consisting of illuminated checkerboards. He had no history of psychiatric disorders or pre-existent cognitive decline.

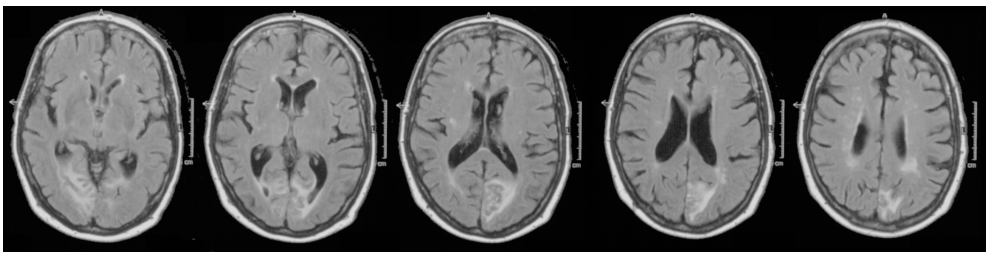

FIGURE 1. MRI scan revealing bilateral occipital infarction.

RZ demonstrated a right-sided hemianopia and standard neuropsychological assessment revealed a normal cognitive status apart from mild memory problems. His main subjective complaint concerned frequently occurring positive visual experiences consisting of coloured and moving persons, faces, and cars. These objects were transparent, smaller than usual, and occurred primarily in his right blind half-field, but sometimes also on the left side. When looking at these objects, they disappeared. These images were very different from his prior auras during migraine attacks and seemed very realistic. The hallucinations disappeared when real stimuli were moving in his surroundings. He experienced these hallucinations continuously and in general found them annoying. He was very much aware of the fact that these positive visual experiences were not real. One week later, he reported that these formed hallucinations were gradually dissipating and that he now experienced primarily unformed flashes of light or colours, again predominantly in the right hemifield.

### PROCEDURE

The frequency (within minutes) of his hallucinations allowed us to investigate the physiological basis using fMRI. The patient was scanned approximately four weeks post-stroke. During scanning he was asked to press a hand-held switch at beginning and end of each hallucination period. This method was similar to the one employed by ffytche, Howard, Brammer, David, Woodruff, & Williams (1998). In addition, the functional status of the remaining cortical tissue of the visual areas was investigated with a checkerboard stimulus, flickering with 2-8 Hz. Flicker rate was alternated every 30 seconds (0, 2, 4, and 8), and image analysis included a factor coding for flicker rate. This parametric design favours selectivity of the statistical map for regions whose activity covaries with flicker rate.

### Image acquisition

FMRI scans were acquired using navigated 3D PRESTO, on a Philips ACS-NT 1.5 Tesla Gyroscan with a PT6000 gradient set (Ramsey et al. 1998), on two separate runs. Scan parameters were: TE/TR 37/26, FOV 225 mm, Flip Angle 9.5, 26 slices each 4 mm thick, scan matrix 64 by 52 by 26, scan time 2.4 s, voxelsize 4 mm. The hallucination experiment lasted 20 minutes (500 scans), during almost half of which the patient indicated having hallucinations (244 scans). The Checkerboard experiment lasted almost 11 minutes (264 scans). Functional scans were followed by a scan with a 30 degree flip angle, which was used as the "anchor" volume for co-registration of functional and anatomical volumes. The session was completed with an anatomical scan (3D-FFE, TE=4.6, TR=30, matrix 128, FOV 256, flip angle 30, slice thickness 1.2 mm, 130 slices). The anatomical scan was used to spatially localise the detected activation. All registration procedures were applied to each dataset separately. Image resolution was preserved by means of tricubic spline interpolation. The 30-degree flip angle functional scan (FA30 scan) was used for registration of the anatomical scan to the functional scans. The functional scans were each registered to the FA30 scan automatically (for details of the procedures see Ramsey et al., 1998). For each subject, the fMRI datasets (i.e. the hallucination and the checkerboard datasets separately) were analysed with a multiple regression analysis. The factor matrix for regression consisted of the factor of interest (one coding the flicker rate for the checkerboard part, and one coding the on-off episodes for the hallucination part). Additional factors were entered into the regression analyses to correct for signal trends (i.e. signal drift across the whole dataset and drift within scan runs). T-values were generated for each voxel, resulting in one hallucination and one flicker t-map. Note that the checkerboard activation map reflects activity that is positively correlated with the changing frequencies of the task.

## Results

First, we set out to investigate the functional status of the primary visual cortices. Bilateral activity was observed in the checkerboard stimulation task compared to no stimulation (Figure 2), suggesting that both primary visual cortices were at least partially intact. These results were highly significant at the $t > 7$ level.

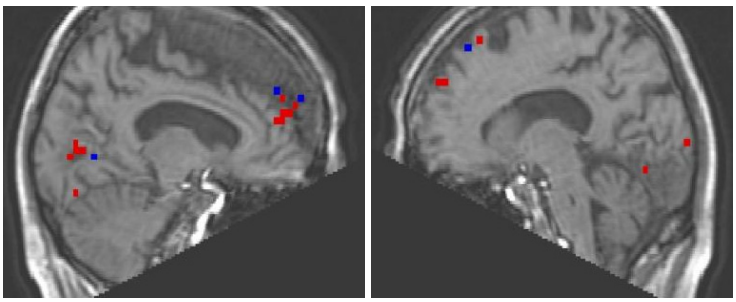

FIGURE 2. Checkerboard stimulation vs. no stimulation (left and right saggital slice through midline).

Subsequently, we looked at those areas that were specifically activated when hallucinations were perceived as compared to baseline scans when no hallucinations were perceived. We limited our search space to the visual cortex, and applied a significance threshold of $p<0.001$, uncorrected (i.e. $t > 3.0$). We observed increased activation in several parts of the visual cortex. Bilateral activation was observed in the calcarine fissure (Figure 3) and medially in the left and right occipital lobe near the lesion sites (Figure 4, white arrows).

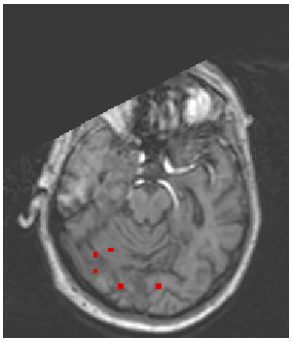

FIGURE 3. Horizontal view. Bilateral activation in the calcarine fissure during hallucinations vs. baseline.

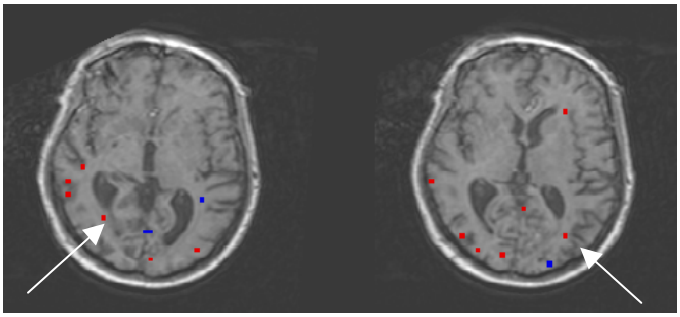

FIGURE 4. Transverse view of visual cortex near lesions (compare slices to second and third slice in figure 1, with slightly different angulation). Arrows indicate activity adjacent to lesion sites during hallucination vs. baseline.

Following the scan session, RZ was questioned about the nature of the hallucinations he experienced in the scanner. He reported that the images he saw consisted mainly of unformed colours and lights, and he perceived objects or faces only occasionally. The total time of hallucinations was approximately half that of the scan time, which provided an optimal contrast for the statistical analysis.

## DISCUSSION

Many patients with visual field defects experience hallucinations. We hypothesised that the origin of these hallucinations is in the primary cortical visual areas close to the lesion that caused the visual field defect. During fMRI scanning, our patient indicated by means of a hand-held switch whether or not he experienced a hallucination. Hallucination-related activity was observed adjacent to infarcted areas in the primary visual cortex in both hemispheres. In a similar vein, previous fMRI studies have shown selective activation in the visual cortex during visual hallucinations in patients with Charles Bonnet syndrome (ffytche et al., 1998), and in a patient with Lewy body dementia (Howard et al., 1997). In a recent study, visual hallucinations disappeared following the application of low frequency repetitive transcranial magnetic stimulation (rTMS) to the occipital cortex of a hemianopic patient (Merabet, Kobayashi, Barton, & Pascual-Leone, 2003). To date, there is no evidence that unimodal visual hallucinations can be generated in subcortical tissue (Braun, Dumont, Duval, Hamel-Hebert, & Godbout, 2003).

The mechanisms underlying this cortical activation during visual hallucinations in neurological patients are still unclear. Most recent theories state that hallucinations, especially complex hallucinations resulting from a focal lesion, are caused by a release of inhibition in the visual cortex because the higher-level "control" areas are damaged (Braun et al., 2003; Manford & Andermann, 1998). This would indicate that the lesioned tissue premorbidly contained an inhibitory predominance over excitatory visual neurons in the association cortices nearby the lesion (Braun et al, 2003). Alternatively, spontaneous activation or irritation of tissue in the vicinity of the lesion (scar tissue) may generate discharges falsely interpreted as due to sensory input, which is the original idea of Seguin in 1886. It has indeed been shown that anticonvulsant treatment abolishes hallucination in some cases (Brust & Behrens, 1977). A final explanation that has been suggested in patients with Charles Bonnet syndrome is that hallucinations arise as a cause of 'sensory deprivation', which may also be a cause of hemianopic hallucination. This deprivation is thought to remove competition with endogenous representations and thus to lower the threshold for hallucination (Braun et al., 2003). However, it has been shown that the lesions causing hallucinations are

significantly smaller that those that cause a hemianopia without any hallucinations (Vaphiades et al., 1996). This suggests that some intact cortex with primary visual processing is required to express hallucinations, and activation in these perilesional areas is shown in the present study. The latter explanation of sensory deprivation is not able to explain this finding, which makes it an unlikely mechanism underlying hallucinations, at least in hemianopic patients.

Finally, a recent case study in a patient with cortical blindness demonstrated that hallucinations dissipated as vision returned (Wunderlich, Suchan, Volkmann, Herzog, Homberg, & Seitz, 2000). This could indicate that hallucination in the early phase of stroke parallels recovery in the severity of hemianopic field defects. Future studies are needed to examine this issue in more detail.

In sum, the present case report demonstrated activation of perilesional brain tissue in the primary visual cortices during hallucinations in a hemianopic patient with bilateral occipital infarction. This pattern of activation is consistent with the proposed mechanisms of either a release of inhibition in the visual cortex, or an irritation of tissue in the vicinity of the lesion. Our findings are similar to earlier fMRI reports in patients with Charles Bonnet syndrome and Lewy body dementia.

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# Conclusions

# Chapter 11

## General Discussion

This thesis entails an extensive study in which a broad range of cognitive domains, including emotional functioning, was carefully assessed in a large population of stroke patients during hospital admission (mean interval eight days post-stroke) and at follow-up six to ten months later. By focusing on specific cognitive and emotional disorders, rather than using global concepts, such as vascular dementia, or one-dimensional screening methods, such as the Mini-Mental State Examination, we were able to explore the neuropsychological sequellae and clinical characteristics associated with these disorders in a detailed manner. This approach enabled us to scrutinise the relative contribution of specific cognitive and emotional disorders in the early phase post-stroke for predicting cognitive outcome, functional outcome, depressive symptoms, and quality of life after the first six months, and to examine the additional predictive value of these cognitive disorders beyond that of other well-known neurological and demographic predictors. Also, we were able to compare the rate of recovery from distinct cognitive disorders and to evaluate which potentially important factors, such as lesion volume, lesion location, pre-existent vascular risk factors, clinical factors at admission, and thrombolytic treatment were associated with cognitive recovery. In addition, the course of depressive symptoms was followed, which allowed us to examine the controversial relation between cognitive impairment and depressive pathology both in the early phase post-stroke and in the long term. Finally, we had the opportunity to study two uncommon cognitive disorders in more detail, i.e. spontaneous confabulations in an amnesic patient with bithalamic brain damage, and complex visual hallucinations in a hemianopic patient who suffered from bilateral occipital infarction.

In this final chapter, I will integrate these findings with reference to the results from other studies. In addition, I will propose some suggestions for clinical practice and discuss the most important methodological considerations and limitations with respect to our study. Finally, some recommendations for future studies will be made.

## INTEGRATION OF MAIN FINDINGS

### PHENOMENOLOGY OF ACUTE COGNITIVE DISORDERS

First, this large-scale study has demonstrated that a neuropsychological examination administered within the first three weeks post-stroke was feasible in 88% of patients with a first symptomatic stroke. On the whole, 80% of patients who suffered from a primary intracerebral haemorrhage and 50% of patients with ischaemic stroke demonstrated cognitive impairment, varying from an isolated disorder to a global impairment involving all cognitive domains *(Chapter 2)*.

The most common acute cognitive disorders were disorders in executive functioning (38%) and visual perception and construction (37%) *(Chapter 2)*. This is probably due to the widespread networks in the brain subserving these cognitive functions (Fassbender et al., 2004; Ganis, Thompson, & Kosslyn, 2004; Vataja et al., 2003), which make them highly vulnerable to brain injury. Memory was not as severely disturbed in this early stage as is often assumed, in line with other recent findings (Rasquin et al., 2004).

In *Chapter 3*, we demonstrated that the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), which is currently the most popular screening tool for cognitive impairment in both clinical practice and scientific research, is not a valid tool to detect cognitive impairment in patients with acute stroke. While most studies adopt a cut-off value of <24 to indicate a disturbed cognition, our findings show that the sensitivity of the MMSE is extremely poor when using this value (34.8%).

### Prognostic implications of acute cognitive disorders

The most important finding of this thesis is that acute cognitive impairment is a powerful independent predictor of a range of adverse outcomes in the long term beyond that of other well-known medical and demographic predictors *(Chapter 4, 5, & 7)*. Interestingly, different cognitive disorders emerged as important predictors of distinct outcome measures, confirming the importance of specifying the nature of cognitive impairment. By using this approach, we can take a closer look at the specific disabilities that might arise from these distinct cognitive deficits.

Domain-specific cognitive performance as assessed during the early phase after stroke predicted the patients' long-term cognitive performance, notwithstanding common stroke-related complications in the early phase such as fatigue, a fluctuating level of arousal, or emotional distress *(Chapter 5)*. This suggests that it is possible to assess the cognitive status in a valid fashion during the initial admission. It should be noted that each domain predicted the performance in the same domain six months later independent of demographic characteristics, except for visual perception and construction. An executive disorder rather than perceptual performance in the early phase of stroke predicted the presence of a long-term perceptual/constructional deficit. The executive functions are considered to be the 'monitor' of other cognitive functions such as memory or attention, which may explain why an acute executive disorder also predicted a long-term impairment in many other cognitive domains *(Chapter 5)*. Moreover, executive dysfunction emerged as the best predictor of long-term cognitive impairment in general *(Chapter 4)* and has been identified as a risk

factor for developing vascular dementia (Pohjasvaara, Mantyla, Ylikoski, Kaste, & Erkinjuntti, 2003; Roman & Royall, 1999).

The term 'executive functioning' and the accompanying impairments are not familiar to many stroke specialists. This term is used as an umbrella for various complex cognitive processes involved in achieving a particular goal, such as planning ahead, inhibiting an action or thought that is irrelevant for current behaviour, adjusting behaviour flexibly to the demands of the environment, or initiating and structuring behaviour (Lezak, Howieson, & Loring, 2004). Although the complexity of the executive functions and the underlying distributed network in the brain make them highly vulnerable to brain injury *(Chapter 2)*, our study also showed that 63% of patients with an initial executive deficit were no longer impaired after six months. In *Chapter 9*, we showed that one particular executive component, i.e. the ability to switch between tasks or thoughts according to the demands of the environment, may be especially important for the occurrence of spontaneous confabulations in amnesic patients. We are currently testing this hypothesis in a group of amnesic patients with Korsakoff's syndrome (Nys & Kessels, in preparation).

Whereas there is an abundance of studies that have shown an association between one specific cognitive disorder and functional disability in stroke patients (Mark, 2003), the relative contribution of cognitive deficits versus each other and beyond that of other well-known medical and demographic variables in the prediction of functional outcome has remained elusive. In the present study, two acute cognitive deficits emerged as the most important predictors of functional outcome after six months, with unilateral neglect being the most important predictor of long-term dependence in basic activities of daily life (ADL), and a disturbed visual perception and construction being the most powerful predictor of long-term dependence in complex ADL *(Chapter 4)*. Interestingly, these same acute disorders were also closely related to depressive symptoms and quality of life after six months. Moreover, the impact of these disorders on the patients' subjectively perceived quality of life was not only restricted to the physical dimension, but was also observed at the mental and social level *(Chapter 7)*.

At first sight it does not seem surprising that these deficits have such devastating consequences in the long term. One of the most important aspects of behaviour is to interact effectively with the environment. Obviously, perceptual systems and the ability to direct attention are crucial in this respect (Lezak et al., 2004). Moreover, it has been extensively demonstrated that perceptual and attentional networks in the brain overlap with neural networks involved in mood (Shenal, Harrison, & Demaree, 2003) and with networks involved in motor action and sensori-motor integration (Freund, 2003). Remarkably, however, the majority of patients with these acute

disorders spontaneously recovered by the time of the follow-up examination. These findings indicate that the adverse outcomes in these patients are not directly related to the persistence of these deficits, in line with previous findings (e.g. Kinsella & Ford, 1985). Until further studies have examined this issue in more detail, we can only speculate as to why these acute disorders have such a profound impact on a variety of outcome measures. The typical pattern of reduced awareness or 'anosognosia' in some of these patients (particularly in patients with a right hemisphere stroke) may have resulted in a less efficient rehabilitation trajectory (Hartman-Maeir, Soroker, Ring, & Katz, 2002). Unfortunately, we did not assess this disorder in the acute phase, mainly due to the lack of instruments to reliably assess anosognosia and because of the heterogeneity of the disorder (Vuilleumier, 2004). In addition, unilateral neglect has also been shown to be a heterogeneous disorder with dissociable subcomponents (Buxbaum et al., 2004) that are most sensitively assessed using a behavioural assessment rather than using a paper and pencil test (Azouvi et al., 2002). Some disabling components may no longer have been assessable after six months with our neuropsychological tasks. With respect to the perceptual domain, the constructional component may have boosted the predictive power, as this ability combines perception with motor response. For example, there is abundant evidence that an impaired performance on constructional tests predicts limitations in important activities such as driving (Gallo, Rebok, & Lesikar, 1999) or meal planning (Neistadt, 1993).

All in all, given the devastating consequences of these disorders (executive functioning, visual perception and construction, and unilateral neglect) in the long term after stroke, these issues certainly await clarification in future trials.

### Cognitive course within the first six months post-stroke

The majority of patients who were cognitively intact immediately after the stroke retained the same level of cognitive performance at follow-up as healthy controls. These findings suggest that there is no evidence of a generalised insidious cognitive deterioration in this stroke population, at least not in the first six months after the stroke. Patients who were cognitively impaired in the early phase of stroke still performed worse than healthy controls at follow-up, especially if multiple cognitive disorders were present at baseline. Although 31% of patients still demonstrated cognitive impairment in at least one cognitive domain after the first six months, improvement as compared to baseline seemed to be the rule rather than the exception. This finding is particularly important, as patients and their caregivers and some general practitioners often assume that cognitive decline cannot be restored

following stroke because of the popular association with dementia. Domain-specific recovery occurred in 41% to 83% of cases, depending on the nature of the cognitive deficit. The prevalence of recovery in our study was much higher than in previous studies, probably related to the fact that our baseline assessment occurred at a much earlier stage leaving more room for improvement. Moreover, in contrast to previous studies (Desmond, Moroney, Sano, & Stern, 1996; Hochstenbach, Den Otter, & Mulder, 2003; Patel, Coshall, Rudd, & Wolfe, 2003), we only included initially impaired patients in our estimation on the prevalence of cognitive recovery. Finally, we studied a relatively mild population of patients with a first-ever stroke without pre-existent cognitive or functional problems, and this population may have a larger potential for recovery of cognitive functions than the stroke population in general (Jorgensen, Nakayama, Reith, Raaschou, & Olsen, 1997).

Taken together, the abovementioned findings are suggestive of an adaptive reorganisation of brain function after stroke. The location of brain plasticity responsible for cognitive recovery is still unclear, with evidence of both peri-lesional changes as well as contralateral reorganisation (Calvert et al., 2000; Perani, Vallar, Paulesu, Alberoni, & Fazio, 1993), most likely also depending on the interval post-stroke and on the nature of the cognitive deficit.

## EARLY RISK FACTORS OF COGNITIVE OUTCOME AFTER STROKE

### *Demographic factors*

It is commonly known that demographic factors exert a strong influence on cognitive functioning and recovery following brain damage (Lezak et al., 2004). This was confirmed in our study, with increasing age and female sex being risk factors of cognitive impairment, and a high education/ high premorbid mental ability being protective factors *(Chapter 2, 4, 5, & 8)*. It has been suggested that a high education or premorbid intelligence provides the brain with a 'reserve' capacity, which makes these subjects better equipped to recruit alternative brain regions to compensate brain pathology (Stern et al., 2003). The underlying neurobiological correlates are still unclear but animal studies have shown that exposure to a complex or stimulating environment results in a greater synaptic density and a more complex neuronal connectivity (Staff, Murray, Deary, & Whalley, 2004). As a result, neuronal interconnections are more redundant which implies more room for recovery following brain damage (Robertson & Murre, 1999).

*Neuro-imaging characteristics*

Patients with a stroke involving the cortex and patients suffering from primary intracerebral haemorrhage were particularly at risk for demonstrating cognitive impairment in the early phase *(Chapter 2)*. However, 46% of patients with subcortical stroke and 43% of patients with infratentorial stroke also demonstrated cognitive impairment in the early phase post-stroke. Previous studies have demonstrated that improvement in perfusion of the overlying cortex in the first days following stroke onset paralleled recovery of cognitive deficits caused by subcortical stroke, indicating that the integrity and efficiency of this cortex is important for recovery (Hillis et al., 2004; Hillis et al., 2002; Vallar et al., 1988). In addition, fMRI studies have consistently shown activation of subcortical and infratentorial structures during various cognitive tasks (e.g. Fink et al., 2000; Ganis et al., 2004; Lewis, Dove, Robbins, Barker, & Owen, 2004). Although the role of subcortical and infratentorial structures in cognition has been increasingly recognised in the scientific literature, cognitive disorders in these patients are frequently overlooked in clinical practice and deserve more attention.

In the longer term, lesion locations involving frontal, parietal, and occipital brain areas were related to a poor recovery in specific cognitive domains *(Chapter 5)*. In addition, a larger lesion volume was associated with an adverse cognitive outcome after six months *(Chapter 4 & 5)*. In this respect, it should be noted that we could not demonstrate a beneficial effect of thrombolytic treatment on cognitive outcome *(Chapter 8)*, although this treatment is thought to result in a reduction of the eventual lesion volume in cases of successful recanalisation. Finally, we found no relation between cognitive outcome and brain pathology that was already present before stroke onset, such as silent infarcts, white matter lesions, or cerebral atrophy *(Chapter 2, 4, & 5)*. It is possible, however, that these factors become increasingly important with respect to cognitive functioning in the longer term after stroke, as has been previously suggested (Gerritsen, 2005).

*Vascular risk factors*

A pre-existent medical history of diabetes mellitus was associated with a poor recovery in one cognitive domain *(Chapter 5)*. The link between diabetes mellitus and poor recovery in post-stroke cognitive functioning (Desmond et al., 1996) and cognitive functioning in general (Biessels, van der Heide, Kamal, Bleys, & Gispen, 2002) has been demonstrated before. The neuroradiological alterations in patients with diabetes mimic those observed in the ageing brain, and therefore it has been suggested that diabetes causes an acceleration of the ageing process in the brain (Biessels et al., 2002). Moderate alcohol consumption before stroke onset was associated with a *better* cognitive outcome, both in the early phase post-stroke *(Chapter 2)* and in the longer

term *(Chapter 4)*. Previous studies also demonstrated a protective effect of moderate alcohol consumption against the development of dementia (Ruitenberg et al., 2002) or cognitive impairment (Stampfer, Kang, Chen, Cherry, & Grodstein, 2005) in non-stroke samples. Several mechanisms have been proposed to explain this effect, with one of the most plausible being the consistently lower rate of cardiovascular disease among moderate alcohol drinkers (Stampfer et al., 2005). The consumption of alcohol may also have psychological benefits in that it is positively associated with the number of social contacts (Adams, 1996).

*Clinical factors at admission*

Fever (hyperthermia) at hospital admission was associated with an adverse cognitive outcome in the early phase and after six months *(Chapter 2 & 4)*. In addition, an increasing admission glucose level was associated with an adverse cognitive outcome after six months. Acute hyperglycaemia and fever have both been shown to result in more severe strokes (Bruno et al., 2002; Kammersgaard et al., 2002) and are risk factors of an adverse functional outcome *(Chapter 4)*. Although these factors did not emerge as *independent* risk factors of cognitive outcome in our study, the early modification of these risk factors may be beneficial for cognitive outcome.

## DEPRESSIVE SYMPTOMS AFTER STROKE

In general, the majority of stroke studies on emotional deficits have reported on the prevalence and determinants of *post-stroke depression*, using a psychiatric diagnosis based on DSM-IV criteria or self-rating scales such as the Beck Depression Inventory. This approach has often resulted in the exclusion of patients with severe cognitive impairment, as diagnostic measures are often not feasible in these patients. However, it has been extensively shown that there is a close relation between depression and cognitive impairment (e.g. Kauhanen et al., 1999; Robinson, Bolla-Wilson, Kaplan, Lipsey, & Price, 1986), suggesting that the patients with the most severe depression may have been excluded in these studies. Moreover, a recent clinical trial demonstrated a resistance to antidepressant treatment in cognitively impaired stroke patients (Spalletta & Caltagirone, 2004). Therefore, in our opinion it is crucial to include particularly those patients in stroke studies on depression.

Whereas only a minority of patients classify as having post-stroke depression, patients frequently show *depressive symptoms* (Henon et al., 2001). Few studies have examined the frequency and determinants of depressive symptoms, and the relationship with cognitive impairment (Verdelho, Henon, Lebert, Pasquier, & Leys, 2004). In the present study, we have examined the prevalence and associates of

depressive symptoms both in the early stage and at six months post-stroke, using an observer-rated measure (Montgomery Åsberg Depression Rating scale) (Montgomery & Asberg, 1979) feasible for use in cognitively impaired patients, which (i) does not draw heavily on somatic symptoms, (ii) has good psychometric properties, and (iii) consists of a small number of items.

We could not find evidence for a relation between the location of the lesion and the presence of depressive symptoms, neither in the acute phase nor in the long term. Hence, we could not confirm the neurobiological model put forward by Robinson and his research group which states that post-stroke depression is caused by left anterior lesions and/ or lesions in the underlying basal ganglia (Robinson, 2003; Robinson, Bolduc, & Price, 1987; Robinson et al., 1986; Robinson, Starr, Kubos, & Price, 1983; Robinson, Starr, Lipsey, Rao, & Price, 1984; Shimoda & Robinson, 1999). This may be due to the fact that we assessed *depressive symptoms* rather than *post-stroke depression*. However, a systematic review (Carson et al., 2000) and more extensive studies on determinants of post-stroke depression (e.g. Carota et al., 2005) could not demonstrate this relation neither. The role of lesion location on the pathogenesis of post-stroke depression might still be identified by prospective studies on very large cohorts, together with innovative neuroimaging methods. Conversely, early cognitive performance was closely related to depressive symptoms both in the early stage and at six months. Although the majority of studies on cognition and depression after stroke have suggested that depression or depressive symptoms may cause cognitive impairment (Kimura, Robinson, & Kosier, 2000; Murata, Kimura, & Robinson, 2000; Narushima, Chan, Kosier, & Robinson, 2003), we could not find evidence for this causal relation *(Chapter 5)*. In contrast, our findings suggest that cognitive impairment may cause or at least aggravate depressive symptoms after stroke *(Chapter 7)*. In addition, we also showed that the degree of functional impairment was closely associated with the severity of depressive symptoms *(Chapter 6)*. Altogether, depressive symptoms after stroke seem to be, at least in part, a psychological reaction to the devastating consequences of stroke, as has been previously suggested (Gainotti, Azzoni, & Marra, 1999; Gainotti et al., 1997; Gainotti & Marra, 2002). Finally, diabetes mellitus and a history of transient ischaemic attack(s) before the stroke independently predicted the presence of depressive symptoms after six months *(Chapter 7)*. Vascular risk factors may thus play a role in exacerbating depressive symptoms in the long term after stroke. These findings are in line with the 'vascular depression' hypothesis which states that chronic cerebrovascular risk factors predispose to or cause depression in vascular compromised patients (Alexopoulos et al., 1997).

## CLINICAL IMPLICATIONS

Major advances have taken place in the past ten years in stroke management, with one of the key changes being the development of the 'stroke unit'. This is a unit specialised in stroke care that consists of a variety of disciplines, such as a medical team, a specialised nursing team, physiotherapists, occupational therapists, speech therapists, and often also a team of social workers (Langhorne & Pollock, 2002). In the acute phase of stroke, the emphasis is on neurological diagnosis and treatment. Subsequently, prevention of accompanying complications and modification of risk factors associated with a recurrent stroke become important issues. After the first days, other disciplines come into play, with physiotherapy and speech therapy being the most important. At present, a neuropsychological examination is rarely performed. Nevertheless, the benefits might be wide ranging, including a better identification of patients at risk for adverse outcome *(Chapter 4, 5, & 7)*, a more appropriate allocation of discharge destination, and a more adequate information provision to other members of the multidisciplinary team, patients, and caregivers (Blake, McKinney, Treece, Lee, & Lincoln, 2002). In addition, previous studies in both animals (Biernaskie, Chernenko, & Corbett, 2004) and humans (Paolucci et al., 2000) have shown that the brain displays a heightened sensitivity to rehabilitation early after stroke as compared to later stages. Therefore, interventions aimed at restoring cognitive functions may also be more beneficial in an early stage, which is only possible if cognitive impairment is detected and specified in an early stage. From a comprehensive review of the empirical literature on cognitive rehabilitation, 62 of 64 controlled studies provided evidence supporting the effectiveness of cognitive rehabilitation (Cicerone et al., 2000). Unfortunately, relatively few studies have directly evaluated the generalisation of treatment effects to everyday situations and behaviours, although several studies provide evidence to support the practical utility of cognitive rehabilitation. For example, it has been shown that patients who received visuo-spatial remediation demonstrated a favourable functional outcome, and subjects treated for executive dysfunction improved their behavioural self-control and problem solving in everyday situations (Cicerone et al., 2000). As these deficits emerged as powerful predictors of adverse outcome in this thesis, cognitive interventions with respect to these deficits may be particularly important for stroke patients. We are currently in the process of evaluating two treatments in the early stage after stroke, i.e. we are comparing the effects of prism adaptation at two weeks with prism adaptation at 3 months in patients with severe neglect (Nys, Dijkerman, van Zandvoort, & De Haan, in preparation), and we are developing a holistic neuropsychological intervention for

patients who are immediately discharged home following their hospital stay (Van Zandvoort, Nys, Kappelle, De Kort, & De Haan, in preparation).

In *Chapter 7*, we have shown that the presence of depressive symptoms in the early stage of stroke is an independent risk factor of depressive symptoms at six months. Therefore, the assessment of mood disturbances early after stroke may help to identify patients at risk for a depressive pathology in the long term. This is particularly important given that there are interventions (such as selective serotonine reuptake inhibitors (SSRIs) or tricyclic antidepressants) which are effective and tolerable in the majority of patients with stroke (Robinson, 2003). Moreover, it has been shown that antidepressant treatment is more effective early after stroke as compared to treatment at later stages (Narushima & Robinson, 2003). In addition, antidepressant treatment has been shown to improve functional outcome (Chemerinski, Robinson, & Kosier, 2001) and to decrease mortality after stroke (Jorge, Robinson, Arndt, & Starkstein, 2003).

In sum, there are several lines of evidence which suggest that an early identification and treatment of cognitive and emotional manifestations in the early stage of stroke may result in a favourable outcome in the long term. Therefore, we recommend the evaluation of these disorders during the patients' stay on the stroke unit, in order to provide an adequate information provision to patients and their caregivers and to optimise discharge destination and intervention programs.

## Methodological Considerations

### Neuropsychological test battery and cognitive domains

We standardised patients' neuropsychological test scores based on the means and standard deviations of a healthy demographically matched control group *(Chapter 2)* because the majority of neuropsychological norm scores were unsuitable for use in our study for the following reasons: (i) We created shorter versions of several neuropsychological tasks in order to compose a feasible neuropsychological test battery for an acute stroke population. However, no norm scores are available for these shorter versions; (ii) Quite a few neuropsychological tasks do not provide adequate age-adjusted or education-adjusted norm scores; (iii) Test-retest reliability is unclear for some neuropsychological tasks. Therefore, we standardised patients' test scores based on the norms and standard deviations of the control performance for the first and second examination separately.

Subsequently, we classified neuropsychological standardised test scores into distinct cognitive domains in order to reduce the amount of neuropsychological

variables and for clinical clarity. We chose to make these classifications a priori according to standard neuropsychological practice (Lezak et al., 2004). The internal consistency for the distinct cognitive domains was adequate (Cronbach's alfa between 0.7 and 1 (Nunnaly, 1978) – *Chapter 2*). This approach allowed us (i) to examine the comparative frequency of distinct cognitive disorders in the early phase after stroke *(Chapter 2)*, and (ii) to study for the first time the relative contribution of the distinct cognitive disorders in the prediction of long-term outcome *(Chapter 4, 5, & 7)*. An alternative approach is to perform orthogonal factor analysis in order to categorise tests based on statistical homogeneity. Whereas this approach would have avoided multicollinearity between cognitive domains (see below), it would have provided less clinically relevant information.

### COGNITIVE IMPAIRMENT AND ZERO-PERFORMANCE

We defined domain-specific cognitive 'impairment' as a domain score below –1.65, which is comparable to the fifth percentile level of control performance (Lezak et al., 2004). This is a more conservative approach compared to prior studies (e.g. Rasquin et al., 2004; Tatemichi et al., 1994). As we were interested in cognitive impairment exclusively related to the stroke, we included a selective stroke population without pre-existent cognitive, neurological, or psychiatric deficits. Moreover, in order to avoid practice effects and statistical artefacts such as regression to the mean, we re-examined the healthy control group with the same time interval between baseline and follow-up as the patients. Therefore, the cognitive disorders that were identified in our patient sample were most likely stroke-related.

Patients who were unable to perform a neuropsychological task in the early stage for whatever reason except for motor deficits were given the minimum score on that task, provided that they were able to perform at least 10 of the 15 tasks. According to this procedure, a zero-performance on a certain task does not necessarily indicate that the underlying cognitive *process* is disturbed, but in any case the patient is unable to perform the *task*. In a few patients with a very selective and severe deficit, a zero-performance may have been given while there was no underlying deficit in that domain, e.g. in patients with selective Broca' s aphasia. Nevertheless, this approach provided excellent prognostic information with respect to long-term cognitive outcome *(Chapter 4-5)* and functional outcome *(Chapter 4)*, indicating that this may be a useful approach for future studies on cognition in the early phase post-stroke.

### Selection bias

Unlike most studies on stroke and cognition, we included patients with ischaemic stroke, as well as patients with primary intracerebral haemorrhage and patients with infratentorial stroke. We also included patients with severe cognitive impairment. By using this procedure, we aimed at the inclusion of a representative sample of patients who survived a first symptomatic stroke. However, the enrolment of patients in the present study was hospital-based, which means that our findings may have been biased towards the more disabled stroke patients (Gerritsen, 2005; Visser-Keizer, 2005) and towards the younger patients (Hollander et al., 2003). Conversely, a community-based study would not have enabled us to record the medical history and neuro-imaging characteristics of the patients.

In longitudinal studies another type of selection bias may also occur through the follow-up of only a selective sample of patients included at baseline. In our study, there were three reasons why patients were not included at follow-up, i.e. (i) because some patients had died between baseline and follow-up, (ii) because we excluded patients who suffered from comorbidity between baseline and follow-up that could potentially affect outcome, and (iii) because we were not able to include some patients because they refused, moved abroad, were in prison, or could not be located at the time of follow-up. An indirect way for examining a potential selection bias is by comparing baseline risk factors between patients included for follow-up and those not included. The patients who were not examined at follow-up had more severe cognitive impairment at baseline than patients who completed follow-up. This selection bias probably resulted in an underestimation of the frequency of impairment on the long term after stroke.

In sum, our findings cannot be directly generalised to the whole population of patients with a first symptomatic stroke. Therefore, validation of our models in similar patient populations is needed in future research.

### Multicollinearity

Determinants may be strongly interrelated, so that if one determinant emerges in a multivariate model it masks the role of another important determinant. For example, performance in one specific cognitive domain is often closely related to performance in another cognitive domain, which may result in the selection of only one of these two determinants. In the regression models performed in this thesis, 95% confidence intervals around odds ratios were typically very wide, which is an additional marker of multicollinarity. Although our approach may have resulted in the elimination of important risk factors, it enabled us to identify a series of powerful predictors in the

early stage that may aid stroke specialists at detecting patients at risk for an adverse outcome.

### CONFOUNDING

Any association between a determinant and an outcome variable may be attributable to a third variable, a so-called confounder. A confounder is associated with both the risk factor and the outcome and is not an intermediate factor in the causal relation between these two variables. A way to deal with confounding is to control for it in statistical analysis. Despite the plethora of studies on the predictive value of cognitive functioning with respect to functional outcome, the potentially confounding influence of well-known medical and demographic factors was never thoroughly examined. Consequently, the prognostic implications of acute cognitive disorders have remained elusive. Although residual confounding may still have been present in our study, this thesis presented the first real attempt to examine the influence of cognition beyond that of other important risk factors of an adverse outcome in the long term after stroke *(Chapter 4,5, & 7)*.

## FUTURE PERSPECTIVES

### CLASSIFICATION OF COGNITIVE DISORDERS

The present study has shown some of the advantages of specifying the nature of cognitive impairment, rather than classifying all cognitive impairment under one header. Particular attention should be given to disorders in executive functioning, visual perception and construction, and neglect. Future research into specific cognitive disorders and the disabilities that might arise from them could provide important information for prognosis and rehabilitation.

### LONGER FOLLOW-UP STUDIES AND REPRESENTATIVE STROKE SAMPLES

Although the largest amount of spontaneous recovery will have taken place within the first six months of stroke, it is possible that cognitive recovery still continues when this time interval has passed. Alternatively, the course of cognitive functioning might change after the first six months, as a recent study has shown that 22% of patients with a stroke or transient ischaemic attack demonstrated a decline in cognitive functioning between 3-6 months post-stroke and after one year (Sachdev, Brodaty, Valenzuela, Lorentz, & Koschera, 2004). Patients should be followed for longer

periods in order to examine the nature of domain-specific cognitive change in the long term.

In addition, future studies on the relation between stroke and cognition are needed in more heterogeneous stroke samples, including patients with recurrent stroke or pre-existent cognitive decline. In *Chapter 3*, the prevalence of cognitive disorders in a patient sample that included patients with a recurrent stroke was much higher (70%), which might indicate that the long-term implications of these disorders are even more devastating in these patients.

### Dynamic brain correlates of cognitive recovery

The introduction of functional neuro-imaging techniques that permit measurement of regional cerebral blood flow, metabolism, or other physiological indices of brain activity in vivo in stroke patients has provided new insights about the cerebral mechanisms of functional recovery. Less attention has been given to dynamic brain correlates of cognitive recovery, with only a few studies that have focused mainly on recovery from aphasia and unilateral neglect. With respect to recovery from aphasia, studies of brain metabolism and perfusion in a "rest" state have emphasised regression from diaschisis in the structurally unaffected regions of the left hemisphere (Pizzamiglio, Galati, & Committeri, 2001). Conversely, activation studies have underlined the increased role of the right hemispheric regions homologous to the language regions of the left hemisphere. A recent case study has shown that recovery from aphasia paralleled a brain reorganisation involving both hemispheres, with an early implication of a new contralesional functional neural network and a later implication of an ipsilesional one (Fernandez et al., 2004). With respect to recovery from unilateral neglect, ipsilesional structures have been shown to be particularly important in mediating recovery (Pizzamiglio et al., 1998). In one of our own studies *(Chapter 10)*, we observed perilesional visual cortex activation during the occurrence of unimodal visual hallucinations in a hemianopic patient. A prior study has shown that hallucinations dissipated as vision returned in a cortical blind patient (Wunderlich et al., 2000). Speculatively, visual hallucinations may be an indicator of visual recovery in patients who suffer from visual impairment due to organic brain damage. Future studies will need to combine metabolic and activation measures prospectively and longitudinally to clarify the relative roles of contralesional and perilesional mechanisms in cognitive recovery.

### Pharmacotherapy and recovery

It has been shown that a rigorous control of vascular risk factors is important in the primary and secondary prevention of dementia, and perhaps even in the improvement from dementia. In addition, acetylcholinesterase inhibitors, such as donepezil or galantamine, may also be efficient in improving cognition in patients with vascular dementia (Erkinjuntti, Roman, Gauthier, Feldman, & Rockwood, 2004). Few studies have examined pharmacological effects on isolated cognitive deficits or milder forms of cognitive impairment that do not classify as vascular dementia. With respect to unilateral neglect, there are several lines of evidence that decreased levels of the neurotransmitter dopamine may be implicated, and that dopamine agonist therapy may reduce neglect both in animals (Corwin et al., 1986; Marshall & Gotthelf, 1979) and in humans (Fleet et al., 1987; Geminiani et al., 1998). Clinical trials studying the cognitive effects of pharmacotherapy are only beginning to emerge, and future placebo-controlled trials are warranted to examine these issues in humans.

Although it has been shown that antidepressant treatment is effective in the majority of patients with stroke, a recent clinical trial has demonstrated that patients with cognitive impairment show resistance to the beneficial effects of antidepressant treatment (Spalletta & Caltagirone, 2004). Transcranial magnetic stimulation (TMS) might be a way to reduce post-stroke depression in these refractory cases (Jorge et al., 2004). In addition, based on the results presented in *Chapter 7*, it might be hypothesised that cognitive remediation and the pharmacological control of vascular risk factors may result in a lower prevalence of stroke patients with depressive pathology.

### Evaluation of neurological treatments with cognition as an endpoint

In *Chapter 8* we evaluated for the first time the long-term effects of thrombolytic treatment with intravenous rt-PA on cognitive outcome. Other neurological and neuro-surgical treatments are increasingly being evaluated using cognition as an endpoint, as it is a sensitive measure related to functional outcome and quality of life. The cognitive evaluation of such treatments may provide important new insights into the usefulness of certain interventions.

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# SUMMARY

Stroke is the third major cause of death and the primary cause of functional disability in Western countries. The incidence rate of stroke in the Netherlands is estimated at 170 to 190 per 100,000 inhabitants per year. This incidence will increase due to ageing of the population and epidemiological transitions. Stroke survivors typically demonstrate a wide range of symptoms. Among the most prominent symptoms are motor deficits, sensory disturbances, and aphasia. These symptoms clearly hamper the patients' everyday life and have received a lot of attention in the literature and in clinical practice. Relatively few studies have focused on the cognitive and emotional manifestations after stroke and these disorders are often overlooked in clinical practice. It is particularly interesting to examine these issues in a large stroke population before neuronal and/or cognitive compensation has taken place. Whereas recovery of function after a stroke is in part attributable to events in the first few days after stroke (e.g. reabsorption of perilesional oedema or tissue reperfusion), consistent reorganisation and recovery usually take weeks to months.

In this thesis, a longitudinal study was performed in a large cohort of patients with a first symptomatic stroke. The patients were admitted to stroke units of three hospitals in the Netherlands (University Medical Centre Utrecht, Tweesteden Hospital Tilburg, and St. Elisabeth Hospital Tilburg) between December 2001 and July 2004. The patient cohort was examined with a mean interval of eight days post-stroke. In addition to a neuropsychological examination covering multiple cognitive domains, demographic data, lesion characteristics, clinical factors at admission, and pre-existent vascular risk factors were recorded. The follow-up examination was administered after six to ten months, in which we examined cognitive outcome, functional outcome, emotional outcome, and quality of life. A demographically matched healthy control group was also examined with the same time interval between baseline and follow-up assessment to obtain a reference sample for the neuropsychological examination.

The first part of this thesis *(Chapters 2-5)* reports a series of studies on the phenomenology, course, and prognostic implications of cognitive disorders in the early phase of stroke.

In *Chapter 2*, the prevalence and nature of acute cognitive disorders were compared between patients with cortical, subcortical, and infratentorial stroke. In addition, clinical determinants of cognitive impairment in the early phase of stroke were examined. We performed a neuropsychological examination within the first three weeks post-stroke, which was feasible in 168 of 190 included patients (88%). In total,

74% of patients with a cortical stroke, 46% of patients with a subcortical stroke, and 43% of patients with an infratentorial stroke demonstrated cognitive impairment in at least one domain. Disorders in executive functioning (39%) and visual perception and construction (38%) were the most common. The prevalence and severity of deficits in executive functioning, language, verbal memory, and abstract reasoning was significantly more pronounced following left cortical stroke compared to right cortical stroke, whereas no hemispheric asymmetry was found following subcortical stroke. Patients with a primary intracerebral haemorrhage and with cortical involvement of the stroke were particularly at risk for developing cognitive impairment in the early phase of stroke, whereas premorbid alcohol consumption of at least two units per day yielded a protective effect.

In C*hapter 3* the sensitivity and specificity of the Mini-Mental State Examination (MMSE) was examined as a tool to detect cognitive impairment in the early phase of stroke. Whereas the Mini-Mental State Examination was originally developed to screen for dementia and delirium, many neurologists use this measure as a screening instrument for 'cognitive impairment' in hospitalised stroke patients. Our study population consisted of 34 consecutively admitted stroke patients and 34 demographically matched healthy controls. The MMSE was administered in addition to a standard neuropsychological examination covering six cognitive domains. Seventy percent of the patients were impaired in at least one cognitive domain based on the neuropsychological examination. Whereas most studies adopt a cut-off value of <24 to indicate impaired cognition in stroke patients, our findings showed that the sensitivity of the MMSE is extremely poor when using this value (34.8%) and particularly insensitive to impairments in abstract reasoning, executive functioning, and visual perception and construction.

In C*hapter 4*, the prognostic value of domain-specific cognitive abilities in acute stroke was evaluated with respect to long-term cognitive and functional outcome, beyond that of neurological and demographic predictors. Overall, 111 of 168 patients who were neuropsychologically examined at baseline were re-examined at follow-up six to ten months later. Thirty-one percent of these patients showed long-term cognitive impairment. Basic and instrumental dependence in daily life remained present in 19% and 24% of patients, respectively. Cognitive functioning at baseline predicted long-term cognitive and functional outcome better than any other variable. Moreover, the prediction of instrumental dependence in daily life improved significantly when cognitive predictors were added to a model consisting solely of medical and demographic predictors. These findings clearly show that an early neuropsychological examination has an additional value compared to current clinical practice in the prediction of outcome. Interestingly, distinct cognitive disorders

predicted different outcome measures. That is, impairments in executive functioning and abstract reasoning were independent predictors of long-term cognitive impairment. Unilateral neglect and visuo-perceptual disorders emerged as the best predictors of long-term functional impairment. These findings demonstrate the importance of characterising the nature of the cognitive disorder rather than studying cognition as a unitary concept.

In *Chapter 5,* the course of cognitive functioning was followed in the same study population, and determinants of domain-specific cognitive recovery were examined. The majority of patients who were cognitively intact immediately after the stroke retained the same level of cognitive performance at follow-up as healthy controls, suggesting that there is no evidence of a generalised insidious cognitive deterioration in this stroke population, at least not in the first six months after the stroke. Conversely, patients who were cognitively impaired in the early phase of stroke still performed worse than healthy controls at follow-up, especially if multiple cognitive disorders were present at baseline. Nevertheless, improvement as compared to baseline performance seemed to be the rule rather than the exception. Recovery in visual perception/ construction and visual memory was the most common (83% and 78%, respectively), whereas recovery in abstract reasoning and language was the least frequent (41% and 54%, respectively). Domain-specific cognitive functioning in the early phase of stroke significantly predicted cognitive functioning in the same domain at follow-up, except for visual perception and construction. These findings confirm that it is useful to assess neuropsychological functioning in such an early stage, and that it may assist in a more adequate discharge decision and rehabilitation planning. Factors associated with poor cognitive recovery were increasing age, lower premorbid cognitive functioning, lesion locations involving the temporal, frontal and occipital lobe, larger lesion volume, and diabetes mellitus.

Emotional disorders, such as depression or apathy, are frequent sequellae of stroke as well. The mechanism by which stroke is associated with depressive pathology remains controversial with two opposing views. Some suggest that there is direct biological mechanism related to the location of the lesion, but others suggest a more indirect psychological mechanism according to which acute stressors associated with stroke are considered the primary cause of depression. Recently, a third view has been proposed which states that not only stroke but chronic cerebrovascular risk factors in general predispose to or cause depression. The second part of this thesis *(Chapters 6-7)* studies the prevalence and clinical determinants of depressive symptoms after stroke. Moreover, the controversial relation between post-stroke cognitive impairment and depressive symptoms is examined in more detail.

In *Chapter 6* the relation between depressive symptoms and specific cognitive functions was scrutinised in patients with a recent stroke, and the relation with lesion characteristics was examined. In general, 40% of patients demonstrated mild and 12% moderate to severe depressive symptoms in the early phase of stroke. The severity of depressive symptoms was related to lesion volume, functional impairment, and cognitive dysfunction. After adjustment for lesion size, a specific neuropsychological profile emerged in patients with moderate to severe depressive symptoms, affecting primarily memory, visual perception, and language. No association was found between severity of depressive symptoms and lesion location, pre-existent lesions and demographic factors.

In *Chapter 7,* the relative contribution of cognitive impairment in the early phase post-stroke was examined as a risk factor for long-term depressive symptoms and reduced quality of life. Depressive symptoms after six months were independently associated with cognitive impairment at baseline, depressive symptoms at baseline, female sex, diabetes mellitus, and previous TIA(s). Cognitive impairment, age, and functional dependence were risk factors for a reduced quality of life, whereas pre-existent hypercholesterolaemia predicted a higher quality of life. Among all cognitive disorders at baseline, unilateral neglect was the greatest risk factor for depressive symptoms after six months, whereas a disorder in visual perception and construction affected quality of life the most. Whereas most previous studies suggest that a depressive pathology after stroke may result in cognitive impairment (the so-called pseudo-dementia), this study shows that cognitive impairment early after stroke may also result in the presence or development of depressive symptoms in the long term. Therefore, it is suggested that depressive symptoms after stroke are, at least in part, a reactive phenomenon secondary to severe cognitive impairment. Moreover, vascular risk factors seem to play a role in exacerbating depressive symptoms in the long term after stroke. These findings are in line with the 'vascular depression' hypothesis which states that chronic cerebrovascular risk factors predispose to or cause depression in vascular compromised patients.

In the third part of this thesis *(Chapter 8)*, we examined whether trombolytic treatment with intravenous recombinant tissue plasminogen activator (rt-PA) administered in the acute phase of ischaemic stroke has a favourable effect on cognitive and functional outcome after six months post-stroke. We included 92 patients with a first-ever symptomatic infarct, of which 25 patients were subjected to rt-PA treatment in the first three hours post-stroke. Multivariate logistic regression analyses adjusted for stroke severity, education, age, and sex were performed to examine whether rt-PA treatment influenced cognitive outcome, basic ADL independence, and instrumental

ADL independence after six months. These findings suggest that thrombolytic treatment is associated with a favourable basic and instrumental ADL outcome, but not with a beneficial cognitive outcome after six months.

Apart from the clinical merits, the neuropsychological assessment in the first weeks post-stroke allowed for the early identification of two patients with uncommon acute cognitive disorders *(Chapters 9-10)*.

In C*hapter 9,* the recovery course of a patient was followed who exhibited an amnesic-confabulatory syndrome in conjunction with severe executive dysfunction in the first week following a bilateral thalamic infarction. Previous studies have shown that spontaneous confabulation originates from the combination of amnesia and executive dysfunction, and that the degree of confabulation is determined by the degree of executive dysfunction. However, a few studies have also reported a dissociation between spontaneous confabulation and executive dysfunction. Therefore, it has been suggested that some, but not all executive components are related to confabulation. In our patient, disappearance of spontaneous confabulation paralleled a specific recovery in mental flexibility, whereas all other executive components and long-term memory remained severely impaired at six months post-stroke. Therefore, this case study suggests that mental flexibility, but not executive functioning in general is related to spontaneous confabulation in stroke patients. However, future studies in larger patient samples are needed to confirm this hypothesis.

In *Chapter 10,* functional magnetic resonance imaging (fMRI) was used to examine the neuro-anatomical correlates of frequent visual hallucinations in a hemianopic patient who suffered from bilateral occipital infarction. By cross-correlating the fMRI data with the hallucination events, we were able to identify the cerebral activity underlying the hallucinations. Bilateral activation was observed in the calcarine fissure and medially in the left and right occipital cortex adjacent to the infarcted areas. This pattern of perilesional visual cortex activation during visual hallucination is consistent with previous fMRI studies in patients with Charles Bonnet syndrome and patients with Lewy Body dementia.

In the final part *(Chapter 11)*, a general discussion is presented comprising an integration of the main findings in this thesis. Some potential implications for clinical practice are reported. Finally, the methodology used in this study is discussed, and some recommendations are made for future research. To conclude, this study has resulted in the following new insights:

1. Cognitive disorders in the first three weeks of stroke are powerful predictors of long-term dependence in daily life, long-term cognitive impairment, and a reduced quality of life, and have additional prognostic value to other well-known medical predictors. Particularly disorders in executive functioning and visual perception and construction predict poor outcome in the long term. We recommend neuropsychological assessment as a standard evaluation on the stroke unit, and plead for a detailed characterisation of the cognitive disorder(s) rather than classifying all impairment under one general header.

2. Until now, it has been suggested that depressive pathology after stroke may result in cognitive impairment (the so-called pseudo-dementia), but our studies show that cognitive impairment in the early stage may also result in depressive symptoms in the long term. Moreover, premorbid vascular risk factors may exacerbate the depressive pathology after stroke.

3. Thrombolytic treatment administered within the first three hours after stroke does not only exert a beneficial effect on basic ADL dependence, as previously demonstrated, but also on more complex ADL dependence such as household management or grocery shopping. Although we could not demonstrate a beneficial effect of the treatment on long-term cognitive outcome, our findings emphasise the need for a revolution in neurologic services with an emphasis on immediate care. Public education is essential in order to learn to recognise a stroke as such and to seek immediate care.

# Samenvatting

Een beroerte of 'cerebrovasculair accident' (CVA) is de derde doodsoorzaak in de westerse wereld en de belangrijkste oorzaak van invaliditeit op oudere leeftijd. Een beroerte kan worden onderscheiden in een hersenbloeding (20%) of een herseninfarct (80%). In Nederland is de incidentie (het aantal nieuwe gevallen) geschat op 170 tot 190 op 100.000 inwoners per jaar. Het toekomstige aantal beroertes zal waarschijnlijk nog toenemen door vergrijzing van de bevolking en andere epidemiologische ontwikkelingen. Als gevolg van een beroerte kunnen verschillende symptomen optreden, afhankelijk van onder andere de locatie en de grootte van de lesie. De symptomen die meest in het oog springen in het vroege stadium na de beroerte zijn stoornissen in de motoriek en de sensibiliteit, afasie, en visuele problemen zoals hemianopsie. Deze stoornissen krijgen dan ook veel aandacht in de klinische praktijk en in wetenschappelijke studies. Naast deze stoornissen kunnen ook cognitieve en emotionele stoornissen worden veroorzaakt door een beroerte. Deze krijgen vaak minder aandacht, met name in de eerste weken na de beroerte. In dit proefschrift wordt een longitudinaal neuropsychologisch onderzoek beschreven waarbij een patiëntenpopulatie die voor het eerst een beroerte heeft doorgemaakt wordt gevolgd in de tijd. Deze populatie is vergeleken met een gezonde populatie op twee meetmomenten. Het eerste onderzoek vond plaats zo kort mogelijk na de beroerte (na gemiddeld acht dagen), en het tweede onderzoek vond plaats na een tijdsinterval van zes tot tien maanden. De patiënten die aan deze studie deelnamen waren opgenomen tussen december 2001 en juli 2004 in het Universitair Medisch Centrum Utrecht, het St. Elisabeth ziekenhuis te Tilburg, of het Tweesteden ziekenhuis te Tilburg. Naast neuropsychologische factoren (zoals cognitieve en emotionele symptomen) werd de invloed van een aantal belangrijke medische factoren onderzocht, waaronder bepaalde lesiekarakteristieken en de medische voorgeschiedenis van de patiënt.

In het eerste deel van dit proefschrift *(Hoofdstukken 2-5)* worden een reeks studies beschreven die ingaan op de fenomenologie, het herstelverloop, en de voorspellende waarde van cognitieve stoornissen in het vroege stadium na een beroerte.

In *Hoofdstuk 2* wordt de prevalentie en de aard van cognitieve stoornissen beschreven die optreden gedurende de eerste drie weken na een beroerte. Ook wordt onderzocht welke factoren te maken hebben met een verstoord cognitief functioneren in dit vroege stadium. In totaal werden 190 patiënten geïncludeerd, waarvan er 168 (88%) onderzocht konden worden met een neuropsychologisch onderzoek binnen de eerste drie weken. Van de patiënten met een corticale lesie vertoonde 74% een

verstoord cognitief functioneren in het vroege stadium, gevolgd door 46% van de patiënten met een subcorticale lesie, en 43% van de patiënten met een lesie in de hersenstam of het cerebellum. Patiënten met een corticale lesie in de linkerhemisfeer vertoonden significant vaker en ernstigere stoornissen in de taal, het verbaal geheugen, het abstract redeneren en de uitvoerende functies dan patiënten met een corticale lesie in de rechterhemisfeer. Er werden geen significante verschillen gevonden met betrekking tot de ernst en frequentie van cognitieve stoornissen tussen patiënten met een linkszijdige of een rechtszijdige subcorticale lesie. Voorts bleek dat met name patiënten met een intracerebrale bloeding en patiënten met corticale betrokkenheid van de lesie een relatief groot risico vertoonden op cognitieve stoornissen in de eerste weken na een beroerte. Patiënten die gewend waren aan een matige alcoholconsumptie vóór de beroerte bleken een minder groot risico te hebben op het vertonen van cognitieve stoornissen in het vroege stadium.

In *Hoofdstuk 3* wordt de sensitiviteit en de specificiteit van de 'Mini-Mental State Examination' (MMSE) als screeningsinstrument voor cognitieve stoornissen geëvalueerd bij patiënten die twee weken eerder een beroerte hadden doorgemaakt. De MMSE is oorspronkelijk ontwikkeld met het oog op de detectie van dementie, maar wordt in de klinische praktijk ook vaak gebruikt om cognitieve stoornissen te screenen na een beroerte. Tot op heden is de MMSE als dusdanig nog nooit gevalideerd. Voor deze studie onderzochten we 34 patiënten en 34 gezonde controles van vergelijkbare leeftijd, opleiding, geslacht, en handvoorkeur. In totaal vertoonden ongeveer 70% van de patiënten een afwijking op één of meerdere cognitieve domeinen zoals gemeten met een uitgebreid neuropsychologisch onderzoek. De MMSE bleek geen goed instrument te zijn voor het detecteren van cognitieve stoornissen, met name omdat geen enkel afkappunt zowel een goede sensitiviteit als specificiteit vertoonde. Vooral stoornissen in het abstract redeneren, de uitvoerende functies, en de visuele perceptie en constructie bleven vaak onopgemerkt door de MMSE.

In *Hoofdstuk 4* wordt de voorspellende waarde geëvalueerd van specifieke cognitieve stoornissen in het vroege stadium na een beroerte op cognitief herstel en de mate van afhankelijkheid in het dagelijks leven na zes maanden. Naast cognitieve predictoren wordt ook de voorspellende waarde onderzocht van andere reeds bekende demografische en neurologische determinanten, zoals de grootte en de locatie van de lesie. Van de 168 patiënten die neuropsychologisch onderzocht konden worden in het vroege stadium konden er 111 nogmaals onderzocht worden na zes maanden. Hieruit bleek dat 31% van deze patiënten nog steeds cognitieve stoornissen vertoonde na zes maanden. Bovendien was 19% nog afhankelijk in basisactiviteiten in het dagelijks leven, zoals het aankleden of zelfstandig eten, terwijl 24% nog steeds afhankelijk was

in meer complexe activiteiten, zoals huishouden of vrijetijdsbesteding. Cognitieve stoornissen in het vroege stadium bleken de beste voorspellers te zijn voor een slechte uitkomst op de langere termijn, zowel wat cognitie betreft als afhankelijkheid in het dagelijks leven. Deze studie toont aan dat vroege neuropsychologische diagnostiek een toegevoegde voorspellende waarde heeft voor het functioneren na zes maanden. Stoornissen in de uitvoerende functies in het vroege stadium waren de sterkste voorspellers voor een verstoord cognitief functioneren op de langere termijn. Daarentegen bleken neglect en stoornissen in de visuele perceptie en constructie de krachtigste voorspellers voor afhankelijkheid in het dagelijks leven. Deze resultaten wijzen op het belang van een gedetailleerde onderkenning van de aard van de cognitieve stoornissen, in plaats van één overkoepelende term voor een verstoord cognitief functioneren zoals 'vasculaire dementie' of 'vasculaire cognitieve stoornis'.

In *Hoofdstuk 5* wordt het herstelverloop gevolgd van de belangrijkste cognitieve functies in dezelfde patiëntenpopulatie met behulp van twee opeenvolgende neuropsychologische onderzoeken met een tijdsinterval van zes tot tien maanden. Daarnaast wordt onderzocht welke factoren herstel van de verschillende cognitieve functies voorspellen. De meerderheid van de patiënten die cognitief ongestoord waren onmiddellijk na de beroerte was dat nog steeds na zes maanden. Echter, de meeste patiënten die wél cognitieve stoornissen vertoonden onmiddellijk na de beroerte bleken op de langere termijn nog steeds verstoord, hoewel er in de meeste gevallen wel vooruitgang zichtbaar was in vergelijking met zes tot tien maanden eerder. Herstel in de hogere visuele functies kwam relatief het vaakst voor (78-83%), terwijl stoornissen in het abstract redeneren en de taal minder goed herstelden (41-54%). Een tweede belangrijke bevinding in deze studie was dat cognitieve stoornissen in het vroege stadium over het algemeen sterke en specifieke voorspellers waren voor het cognitief functioneren in hetzelfde domein op de langere termijn, behalve wat betreft visuele perceptie en constructie. Deze bevindingen tonen aan dat het zinvol is om een neuropsychologisch onderzoek te doen in een vroeg stadium. Hiermee kunnen de ontslagbestemming en het revalidatietraject mogelijk adequater bepaald worden. Leeftijd en premorbide cognitief functioneren bleken onafhankelijke voorspellers voor cognitief herstel in meerdere cognitieve domeinen, net zoals lesies in de temporale en occipitale hersengebieden. De grootte van de lesie, de aanwezigheid van diabetes mellitus vóór de beroerte, en een lesie in de frontaalkwab bemoeilijkten cognitief herstel in één domein.

Naast cognitieve stoornissen komen ook vaak emotionele stoornissen voor na een beroerte, zoals depressie of apathie. Er bestaat momenteel nog steeds onenigheid in de literatuur over de onderliggende mechanismen waardoor depressie tot stand komt

na een beroerte. Sommige eerdere studies hebben aangetoond dat de locatie van de lesie sterk samenhangt met depressie, wat wijst op een biologisch mechanisme. Andere onderzoekers stellen daarentegen dat depressie na een beroerte niets anders is dan een psychologische reactie op het doormaken van een acute, levensbedreigende aandoening. Recentelijk stelde een derde theorie dat niet enkel een beroerte maar cerebrovasculaire risicofactoren in het algemeen samenhangen met of leiden tot depressie. In het tweede deel van dit proefschrift *(Hoofdstukken 6-7)* zijn de prevalentie en klinische determinanten van depressieve symptomen die voorkomen na een beroerte onderzocht. Daarnaast wordt dieper ingegaan op de relatie tussen cognitieve stoornissen en depressieve symptomen.

In *Hoofdstuk 6* wordt onderzocht welke neuropsychologische en neurologische factoren samenhangen met de ernst van depressieve symptomen in het vroege stadium na een beroerte. Veertig procent van de patiënten vertoonde milde depressieve symptomen, en twaalf procent vertoonde matige tot ernstige depressieve symptomen. De ernst van de depressieve symptomen was gerelateerd aan de grootte van de lesie, de mate van afhankelijkheid tijdens ziekenhuisopname, en de ernst van de cognitieve stoornissen in dit vroege stadium. Patiënten met matige tot ernstige depressieve symptomen vertoonden een significant slechtere prestatie met betrekking tot het geheugen, de visuele perceptie en constructie, en de taal dan patiënten met milde depressieve symptomen of patiënten zonder deze symptomen. Er werd verder geen relatie aangetoond tussen de ernst van de depressieve symptomen en de locatie van de lesie.

In *Hoofdstuk 7* wordt de relatieve bijdrage onderzocht van vroege cognitieve stoornissen in het voorspellen van depressieve symptomen en de kwaliteit van leven op de langere termijn, naast de invloed van vasculaire risicofactoren, neurologische factoren, en demografische variabelen. Depressieve symptomen en een verstoord cognitief functioneren in het vroege stadium, vrouwelijk geslacht, diabetes mellitus en TIA's in de voorgeschiedenis kwamen naar voren als onafhankelijke voorspellers van depressieve symptomen op de langere termijn. Daarentegen bleken een verstoord cognitief functioneren, afhankelijkheid tijdens ziekenhuisopname en hogere leeftijd onafhankelijke voorspellers voor een verminderde kwaliteit van leven na zes maanden, terwijl hypercholesterolaemie in de voorgeschiedenis een betere kwaliteit van leven voorspelde. Van alle cognitieve stoornissen bleek neglect in het vroege stadium het sterkst samen te hangen met depressieve symptomen na zes maanden, terwijl een stoornis in de visuele perceptie en constructie het sterkst geassocieerd bleek met de kwaliteit van leven. Naast het feit dat eerdere studies over het algemeen suggereren dat depressieve symptomen kunnen leiden tot cognitieve stoornissen (een zogenaamde pseudo-dementie) toont deze studie aan dat een verstoord cognitief functioneren in

het vroege stadium ook kan resulteren in depressieve symptomen op de langere termijn. Bovendien lijken vasculaire risicofactoren ook bij te dragen tot het instandhouden van depressieve symptomen op de langere termijn.

In het derde deel van dit proefschrift *(Hoofdstuk 8)* wordt onderzocht of en in welke mate een behandeling met een trombolyticum (c.q. recombinant tissue plasminogen activator [rt-PA]) binnen de eerste drie uur na het ontstaan van de eerste symptomen de cognitie en de mate van afhankelijkheid in het dagelijks leven na zes maanden verbetert. In deze studie werden 92 patiënten geïncludeerd, waarvan er 25 (27%) een behandeling kregen met rt-PA. Multivariate logistische regressie gecorrigeerd voor leeftijd, opleiding, geslacht en ernst van de beroerte toonde aan dat patiënten die behandeld waren met rt-PA minder afhankelijk waren in het dagelijks leven na zes maanden, zowel op basisactiviteiten als op meer complexere activiteiten. De behandeling leek echter niet van invloed te zijn op het cognitief functioneren na zes maanden.

Zoals reeds aangegeven herstellen veel patiënten die voor het eerst een beroerte hebben gehad grotendeels van hun stoornissen. Dit betekent dat sommige cognitieve stoornissen slechts korte tijd blijven bestaan. In het vijfde deel van dit proefschrift *(Hoofdstukken 9-10)* beschrijven we twee patiënten met uitgesproken cognitieve stoornissen die specifiek voorkomen in de eerste weken na een beroerte.

In *Hoofdstuk 9* wordt het herstelverloop gevolgd van een amnestische patiënt die gedurende de eerste twee weken na het doormaken van een bilateraal thalamusinfarct spontane confabulaties en een ernstige stoornis in de uitvoerende functies vertoonde. Spontane confabulaties zijn verzinsels die vaak een absurde inhoud hebben, die spontaan geuit worden, en waarnaar ook gehandeld wordt. Eerdere studies hebben aangetoond dat spontane confabulaties meestal voorkomen bij patiënten die zowel amnesie vertonen als een stoornis in de uitvoerende functies hebben. Andere studies hebben echter dissociaties aangetoond tussen spontane confabulaties en executief dysfunctioneren in amnestische patiënten. Mogelijk is deze discrepantie te wijten aan het feit dat de 'uitvoerende functies' een conglomeraat zijn van uiteenlopende subcomponenten, waarbij sommige, maar niet alle componenten gerelateerd zijn aan confabuleren. In onze gevalsstudie bleek dat de patiënt naast het verdwijnen van de spontane confabulaties na zes maanden ook hersteld was op één specifieke component van de uitvoerende functies, namelijk de 'mentale flexibiliteit', terwijl hij nog steeds ernstige afwijkingen vertoonde op alle andere uitvoerende taken en geheugentests. Deze bevindingen suggereren dat specifiek deze uitvoerende

component samenhangt met spontane confabulaties. Verder onderzoek is echter nodig om deze hypothese te bevestigen.

In *Hoofdstuk 10* wordt een patiënt beschreven die in het vroege stadium na het doormaken van een bilateraal occipitaal herseninfarct visuele hallucinaties vertoonde in zijn blinde halfveld (homonieme hemianopsie). Twee eerdere studies hebben door middel van functionele beeldvorming aangetoond dat visuele hallucinaties bij patiënten met het Charles Bonnet syndroom en Lewy-body-dementie samenhangen met corticale activatie in de primaire visuele cortex. Het is echter onduidelijk welke hersengebieden actief zijn tijdens visuele hallucinaties bij patiënten met laesies in deze hersengebieden. In deze tweede gevalsstudie toonde de patiënt tijdens het hallucineren een bilaterale activatie in de calcarine fissuur in zowel de linker als rechter occipitale cortex naast de geïnfarceerde gebieden, in overeenstemming met de eerdere beeldvormingsstudies.

In het laatste deel *(Hoofdstuk 11)* worden de belangrijkste bevindingen in dit proefschrift geïntegreerd. Enkele mogelijke implicaties voor de klinische praktijk en voor toekomstig onderzoek worden besproken, en de sterke en zwakke punten van de methodologie van deze studie worden nader bekeken. Concluderend kan gesteld worden dat het onderzoek in dit proefschrift heeft geleid tot de volgende nieuwe inzichten:

1. Cognitieve stoornissen in het vroege stadium na een beroerte zijn sterke voorspellers voor afhankelijkheid in het dagelijks leven en een verstoord cognitief functioneren op de langere termijn, voor een verminderde kwaliteit van leven, en voor depressieve symptomen na zes maanden, onafhankelijk van andere medische voorspellers. Vooral stoornissen in de uitvoerende functies en in de visuele perceptie en constructie voorspellen een slechte uitkomst op de langere termijn. De bevindingen in dit proefschrift pleiten voor een neuropsychologisch onderzoek als standaard onderzoek op de stroke unit. Bovendien blijkt uit onze resultaten dat cognitieve stoornissen wel degelijk gespecificeerd kunnen worden in het vroege stadium na een beroerte, en dat dit de voorkeur heeft boven het gebruik van een overkoepelende term voor alle cognitieve functiestoornissen.

2. Meestal wordt gesuggereerd dat depressieve symptomen mogelijk kunnen leiden tot cognitieve stoornissen. Onze studies toonden echter aan dat het omgekeerde ook het geval kan zijn. Bovendien lijken vasculaire risicofactoren ook een rol te spelen in het veroorzaken of versterken van depressieve symptomen na een beroerte.

3. Met dit onderzoek hebben wij voor het eerst aangetoond dat een behandeling met trombolyse binnen de eerste drie uur na een beroerte niet enkel kan leiden tot een grotere onafhankelijkheid na 6 maanden in basisactiviteiten zoals persoonlijke hygiëne

of zelfstandig toiletgebruik, maar ook in complexere activiteiten, zoals boodschappen doen, schoonmaken, en vrijetijdsbesteding. Dit geeft aan dat informatiecampagnes over de symptomen van een beroerte en het belang van een snelle ziekenhuisopname kunnen bijdragen aan een optimale behandeling, en daardoor kan leiden tot een beter herstel op de langere termijn.

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Liefs, Gudrun
April 2005

# Curriculum Vitae

Gudrun Nys werd geboren op 31 oktober 1977 te Roeselare (België). In 1995 behaalde zij het diploma Latijn-Moderne Talen aan het Bisschoppelijk Lyceum der Grauwe Zusters in Roeselare. In datzelfde jaar is zij gestart met de opleiding Psychologie aan de Katholieke Universiteit Leuven. In 1999-2000 deed zij haar onderzoeksstage aan de Universiteit van Birmingham (School of Psychology). Zij behaalde het diploma 'licenciaat in de psychologie' in 2000 in de richting Theoretische Psychologie (onderzoekspakketten functieleer en fysiologie). In hetzelfde jaar werd zij aangesteld als onderzoeker (A.A.P.) aan de Katholieke Universiteit Leuven (Laboratorium Experimentele Psychologie). Zij was in dat jaar tevens werkzaam als neuropsychologe in het St. Rafaël ziekenhuis te Leuven waar zij diagnostiek deed bij kinderen en volwassen met visuele stoornissen. In 2001 werd zij als junior onderzoeker aangesteld bij het Universitair Medisch Centrum Utrecht en de capaciteitsgroep psychonomie van de Universiteit Utrecht, waar zij sinds die tijd promoveert. Sinds mei 2004 is zij als junior docent/onderzoeker Neuropsychologie verbonden aan dezelfde capaciteitsgroep.

Gudrun Nys was born on October 31, 1977 in Roeselare (Belgium). In 1995 she completed her secondary school education at the 'Bisschoppelijk Lyceum der Grauwe Zusters' in Roeselare. In the same year, she commenced her psychology education at the Catholic University of Leuven. In 2000 she finished her research internship at the University of Birmingham (School of Psychology). She obtained her psychology degree in 2000 and was appointed in the same year as a research fellow at the Catholic University of Leuven (Department of Experimental Psychology). In addition, she worked as a neuropsychologist at the St. Rafaël hospital in Leuven (department of ophthalmology). In 2001, she was appointed as a PhD student at the University Medical Centre Utrecht and the department of psychonomy of the Utrecht University. In May 2004, she was appointed as a lecturer/researcher in neuropsychology in the same department.